



# THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

### Variation in recombination frequency and distribution across eukaryotes

**Citation for published version:**

Stapley, J, Feulner, PGD, Johnston, SE, Santure, AW & Smadja, CM 2017, 'Variation in recombination frequency and distribution across eukaryotes: patterns and processes', *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 372, no. 1736. <https://doi.org/10.1098/rstb.2016.0455>

**Digital Object Identifier (DOI):**

[10.1098/rstb.2016.0455](https://doi.org/10.1098/rstb.2016.0455)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Peer reviewed version

**Published In:**

Philosophical Transactions of the Royal Society B: Biological Sciences

**Publisher Rights Statement:**

& 2017 The Authors. Published by the Royal Society under the terms of the Creative Commons Attribution License <http://creativecommons.org/licenses/by/4.0/>, which permits unrestricted use, provided the original author and source are credited.

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



**Variation in recombination frequency and distribution across Eukaryotes: patterns and processes.**

Jessica Stapley<sup>1</sup>, Philine G. D. Feulner<sup>2,3</sup>, Susan E. Johnston<sup>4</sup>, Anna W. Santure<sup>5</sup> and Carole M. Smadja<sup>6</sup>

<sup>1</sup> Centre for Adaptation to a Changing Environment, IBZ, ETH Zürich, Switzerland.

<sup>2</sup> Department of Fish Ecology and Evolution, Centre of Ecology, Evolution and Biogeochemistry, EAWAG Swiss Federal Institute of Aquatic Science and Technology, Switzerland

<sup>3</sup> Division of Aquatic Ecology and Evolution, Institute of Ecology and Evolution, University of Bern, Switzerland

<sup>4</sup> Institute of Evolutionary Biology, University of Edinburgh, United Kingdom.

<sup>5</sup> School of Biological Sciences, University of Auckland, New Zealand.

<sup>6</sup> Institut des Sciences de l'Évolution UMR 5554 (CNRS, IRD, EPHE, Université de Montpellier), France.

Keywords: crossing over, meiosis, genetic linkage, evolution, adaptation, genomic architecture

## Abstract

Recombination, the exchange of DNA between maternal and paternal chromosomes during meiosis, is an essential feature of sexual reproduction in nearly all multi-cellular organisms. While the role of recombination in the evolution of sex has received theoretical and empirical attention, less is known about how recombination rate *itself* evolves and what influence this has on evolutionary processes within sexually reproducing organisms. Here, we explore the patterns of, and processes governing recombination in Eukaryotes. We summarise patterns of variation, integrating current knowledge with analysis of linkage map data in 353 organisms. We then discuss proximate and ultimate processes governing recombination rate variation and consider how these influence evolutionary processes. Genome-wide recombination (cM/Mb) rates can vary more than 10-fold across Eukaryotes, and there is large variation in the distribution of recombination events across closely related taxa, populations and individuals. We discuss how variation in rate and distribution relates to genome architecture, genetic and epigenetic mechanisms, sex, environmental perturbations and variable selective pressures. There has been great progress in determining the molecular mechanisms governing recombination, and with the continued development of new modelling and empirical approaches there is now also great opportunity to further our understanding of how and why recombination rate varies.

## 1. Introduction

Recombination is the exchange of DNA between maternal and paternal chromosomes during meiosis, and is a fundamental feature of sexual reproduction in nearly all multicellular organisms, producing new combinations of genetic variants or alleles which are passed on to offspring. It is also a fundamental, yet paradoxical evolutionary process: it can facilitate adaptation through the creation of novel genetic combinations, but it can also break apart favourable combinations of alleles, potentially reducing fitness [1-3]. This antagonism is central to the adaptive responses of organisms to their environment [4, 5], but also to the evolution of sex [3, 6] and to the formation of new species when there is gene flow [7, 8]. Recombination also performs an essential role during meiosis to ensure accurate segregation of chromosomes [9, 10]. As a consequence, tight regulation of the rate of recombination is expected, but studies have revealed that recombination can vary within and between chromosomes, individuals, sexes, populations and species [11-15]. Recombination rates can be influenced by environmental and demographic factors, but are also heritable and underpinned by specific genetic loci [16-20] and can respond to selection [21, 22]. Therefore, they have the potential to vary in a manner dependent on the evolutionary or selective contexts [6]. While the role of recombination in the evolution of sex and in facilitating responses to selection has been the focus of much empirical and theoretical work, investigation on how recombination rate *itself* evolves and how this impacts evolutionary processes within sexually reproducing organisms has received less attention. Until recently, empirical studies were restricted to cytogenetic studies of chiasma counts, or to low-density linkage map data in a handful of model organisms; however, in recent years, advances in genomic technologies have allowed more detailed characterisation of recombination rates at a finer genomic scale and in a greater number of species.

In this review, we aim to explore the patterns of, and processes governing recombination in predominantly sexually reproducing Eukaryotes from an evolutionary perspective, in a manner that is accessible to a general audience. We begin by summarising the patterns of variation in the number of recombination events in the genome per megabase per generation (herein referred to as recombination rate) at different taxonomic and genomic scales across Eukaryotes – updating and integrating current knowledge with an analysis of

linkage map data in 353 organisms. Then, we discuss processes governing recombination rate variation, beginning with what is known of the proximate causes and genetic correlates of recombination rate variation, before summarising the key evolutionary (ultimate) causes and consequences of this variation. We do not attempt to systematically review the enormous body of literature, but want to provide the reader with an introduction to the topic that is taxonomically broad, reflecting the development of the field, and provide directions for future research. Throughout, we use the term recombination to refer to the meiotic process whereby a double strand DNA break (DSB) is repaired via reciprocal exchange of genetic material between homologous chromosomes, resulting in a crossover (CO).

## **2) Patterns of variation in recombination**

Recombination can be compared at different taxonomic scales and at different genomic resolutions, and information at these different scales provides opportunities to address different questions about how and why recombination rate varies (Figure 1). Recent advances in DNA sequencing technologies and in methods to estimate recombination rate from genetic variation data (polymorphisms) sampled from a population have facilitated estimates of genome-wide recombination rate (GwRR) across species and provided new opportunities to determine the distribution of recombination at a finer genomic scale (see Box 1). A pervasive pattern to emerge from these studies is that recombination events are distinctly non-random, and two important patterns are recognised. Firstly, the exchange of DNA during a CO event at a location on the chromosome (known as a chiasma) tends to suppress the creation of nearby chiasma, in a process known as CO interference [23], and secondly, recombination events are often localised into narrow regions, termed hotspots, where recombination is an order of magnitude (2-10x) higher than the average. Hotspots have been observed in a range of organisms e.g. *Saccharomyces* yeast [24], fungal pathogens [25], plants [see 26], mammals [27], and birds [28], but are absent from others, e.g. *Caenorhabditis elegans* [29], honey bees [30] and *Drosophila* [see 31, 32]. Studies across different taxonomic scales have shown that recombination frequency and landscape may be controlled by different mechanisms in different taxa. Consequently, describing how recombination frequency and landscape vary at different taxonomic scales, from distantly-

related taxa to individuals, is a key step toward understanding their rate of evolution as well as their proximal and ultimate correlates.

## **2a) Variation across distantly related Eukaryote taxa**

There have been several comparisons of GwRR per base, kilobase (Kb) or megabase (Mb) across distantly related taxa [33-36]. The most striking pattern to emerge was that microorganisms and fungi have much higher recombination rates compared to animals and plants [33, 34]. However, these studies were carried out in a relatively small number of species, often relying on chiasma count data in a single sex. Therefore, we compiled data on linkage map length, haploid chromosome number and genome size from all the major groups of Eukaryotes, to provide a more comprehensive and up-to-date picture of recombination rate variation. Details of the methods and data are provided in the electronic supplementary material, and a summary of the species included in our dataset is in Table 1 (see electronic supplementary material for full list). Briefly, we obtained sex average linkage map lengths, genome size and haploid chromosome number from the published literature and public databases. In cases where a species had multiple maps we chose the map with the most markers or the most individuals in cases where two maps had a similar number of markers. We omitted linkage maps with <50 markers and where the number of linkage groups (LG) and the haploid chromosome number (HCN) differed markedly (absolute(LG-HCN)/HCN > 0.7). In our analyses, we controlled for phylogeny by fitting a Phylogenetic Generalized Linear Model with the R Package 'Caper' [37]. The phylogeny was obtained using the Phylotastic Web Service ([https://github.com/phylotastic/phylo\\_services\\_docs/blob/master/ServiceDescription/PhylotasticServicesDescription.md](https://github.com/phylotastic/phylo_services_docs/blob/master/ServiceDescription/PhylotasticServicesDescription.md)), which extracts a Supertree from openTree [38]. All branch lengths were set to 1 in the Supertree. In total, we obtained data for 353 species, across Animals, Plants, Fungi and the SAR (Stramenopiles-Alveolates-Rhizaria Eukaryote) supergroup. Not surprisingly, there is a bias towards model species, domestic and crop species, and parasitic or disease causing species, for which QTL studies have been the focus of much research.

To estimate GwRR from linkage map data we divided the linkage map length (the sum of the length of all sex-averaged linkage groups) by the haploid genome size (in Mb), Box 2 Figure

2). This is a commonly reported measure of recombination rate [11, 33, 34, 39-41] and provides a useful metric to compare across taxa with vastly different genome sizes. This measure averages recombination across both the open and transcriptionally active euchromatic region and the closed and inactive heterochromatic regions of the genome. Recombination is often suppressed in heterochromatic regions, and the strength of suppression and the proportion of the genome that is heterochromatic varies greatly between organisms [see 42]. Thus, GwRR represents a genome average that reveals differences in recombination rate, but will be related to differences in the amount of heterochromatin in the genome and how strongly recombination is suppressed in these regions. Taking account of the proportion of the genome that is heterochromatic may provide more informative estimates of recombination with respect to evolutionary processes [41, 42], however this data is only available for relatively few organisms, so we have not included it in this analysis. Overall our analysis confirms the previously reported pattern of higher GwRR in Fungi and SAR compared to Plants and Animals, but also provides estimates for new taxonomic groups (Figures S1-S3) and opportunities to begin to address enduring questions about the evolution of recombination rate (Figure 1).

In contrast to comparing recombination rate across distantly related taxa, comparisons within specific taxonomic groups are more common (i.e. mammals [43], plants [39, 41, 44, 45], homopterous insects [46] and hymenoptera [47]), and several notable patterns have been identified. For example, amongst insects, social hymenoptera have much higher recombination rates [33]; amongst mammals, marsupials have lower recombination rates [48]; and amongst plants, conifers have very low recombination rates [39]. Comparing within taxonomic groups in our data we also observed these patterns and make several new observations; amongst Crustaceans, the Cladocerans (represented by two species of *Daphnia*) have much higher recombination rates (electronic supplementary material Figure S1), Dipterans have the lowest rates of recombination rate across insects (electronic supplementary material Figure S1) and fishes have the highest recombination rate amongst vertebrates (Figure 2).

## **2b) Variation among closely related taxa and between populations within species**

Linking variation in recombination rates between closely related species and between populations with variation in selection and demography may elucidate long-term mechanisms driving recombination rate evolution. Differences in chiasma count between sister species, populations, accessions and inbred lines of cultivated and model species have been studied since the 1930s [e.g. 49, 50-52]. Within a more ecological context (i.e. natural populations, non-model species), early empirical work identified relationships between chiasma frequency and ecological and environmental variables. For example, chiasma frequency per bivalent (Cf/B) in Orthopterans is associated with latitude [see 15], was higher in low density populations of grasshoppers [53] and snails [54], and in plants Cf/B was higher in selfers compared to outcrosses [55, 56]. In many cases where clinal variation in recombination has been detected, karyotypic differences, which are known to modify recombination, are also present (e.g. accessory or B chromosomes [see 15, 54], chromosomal inversions [54]). These karyotypic differences can suppress GwRR and may explain the variation observed. At a finer genomic scale, comparisons between closely related taxa find, in general, greater variation in the recombination landscape compared to the GwRR. For example, similar linkage map lengths are evident across species (e.g. *Eucalyptus* [57], flycatchers (*Ficedula*) [58]), strains (e.g. *Caenorhabditis briggsae* [59]), cultivars (e.g. maize (*Zea mays*) [60]) and populations (e.g. great tit (*Parus major*) [61], honey bee (*Apis mellifera*) [62]). In most mammals, the position of hotspots appears to be dynamic, differing between subspecies of mice [63] and between humans and chimps [64], while hotspot location is more conserved in other groups, for example birds [28, 58], dogs [65] and in *Saccharomyces* yeast [66]. Recent work in determining the molecular mechanisms governing hotspot activity has shed light on this pattern, most notably, in species with rapidly evolving hotspots, hotspot position is determined by a common gene (PRDM9), whereas this gene is missing or non-functional in species with more conserved hotspots [67 and discussed in Section 2].

## **2c) Variation in recombination between the sexes**

The most widely reported within-species variation in recombination rate is that seen between the sexes. Differences between sexes can be as extreme as one sex lacking recombination completely (achiasmy), or where recombination is present but different in both sexes, in terms of the rate and landscape (heterochiasmy), [68]. Achiasmy has evolved



independently at least 26 times [15, 69, 70] and nearly always occurs in the heterogametic sex (e.g. in XY *Drosophila* males and ZW *Bombyx* females) [71-73]. By contrast, heterochiasmy is phylogenetically dispersed across plants and animals, and reduced recombination is not always observed in the heterogametic sex [68, 69]. In animals and plants, females tend to have higher overall rates of recombination, although exceptions exist, such as in corals, marsupials, macaques and sheep [68, 74, 75]. There appears to be no link between sex chromosomes or sex determining mechanism (genetic, environmental) and the direction of heterochiasmy. However, only one species that has environmental sex determination (ESD) has been studied to date, and more studies are needed in clades that have evolved ESD multiple times (e.g. lizards and turtles) to test this more explicitly.

#### **2d) Variation in recombination between individuals**

Examination of recombination at the individual level, using cytogenetic and pedigree-based approaches, has shown that genome-wide recombination rates can vary substantially between individuals within a population. Studies in humans, cattle, sheep, mice and *Drosophila* have shown that variation in regional or genome-wide recombination rates (cM/Mb) often have an underlying heritable component, explaining 8 – 40% of the phenotypic variance in rate [16-18, 76, 77]. Mammalian studies have identified meiotic genes that consistently underlie rate variation, notably ring finger protein 212 (*RNF212*); studies at finer genomic scale e.g. in humans and cattle have also exposed heritable differences in recombination landscape and hotspot usage mediated by variation in *PRDM9* [18, 78]. We explain these genetic mechanisms driving heritable variation in more detail in Section 3b.

#### **2e) Variation within individuals**

Variation in recombination rate has been observed within individuals, i.e. between subsequent measurements or between clones experiencing different environments, demonstrating plasticity in recombination rate. Intrinsic factors, such as age and stress, as well as a diverse range of extrinsic factors, such as parasites, have been found to influence crossover frequency [79-81]. Of all studies to date, there are three commonly reported factors affecting recombination rate within individuals.

The first, age, has been considered in several model species, but there is little consensus in broad trends. In humans, recombination rate (cM/Mb) tends to increase with maternal age, whilst there appears to be little effect of paternal age (see [82] and references therein, for an exception see [83]); in mice, patterns in females and males are varied [84-87]. In *Arabidopsis thaliana* paternal recombination rate (cM/Mb) measured at nine genomic intervals was stable in five of these regions, but increased with age in the other four [88]. In cattle and humans, crossover interference, which can set a minimum distance between neighbouring crossovers, decreases with maternal age, which may explain observed increases in recombination frequency [86, 89].

Secondly, temperature is one of the most commonly reported extrinsic correlates of recombination rate variation. In exothermic organisms, successful completion of meiosis is sensitive to changes in temperature, which are frequently associated with failures in synapsis and subsequent declines in fertility [see 90]). The relationship between increasing temperature and crossover number and positioning varies across species; for example in plants, it is associated with increased paternal recombination in *Arabidopsis* and barley (*Hordeum vulgare* L.), but decreases in other species (e.g. *Allium ursinum*, *Locusta migratoria*) [see 79]. Relationships can also vary non-linearly with temperature, such as in *Drosophila*, where the highest recombination rates occur at both high and low temperature extremes [see 90]). Interestingly, temperature can also influence the degree of heterochiasmy; in barley, at 10°C sex specific rates of recombination (cM/Mb), estimated from linkage maps, were similar with a male/female map length ratio of 1.02, but at 30°C this ratio increased to 1.58 [91].

The third extrinsic factor frequently associated with variation in recombination rate is pathogen infection. In line with predictions of the Red Queen hypothesis - enhanced recombination rates will increase the genetic diversity of offspring, so that more rapidly evolving parasites cannot exploit a static host genotype [92] - studies have observed longer linkage maps, increased recombination frequency and rate (cM/Mb) with parasite infection; e.g. *Tribolium castenatum* [93, 94], *Arabidopsis* [95] and tomato and barley [96], but see other studies in e.g. mice [97] and *T. castenatum* [98]). A study in *D. melanogaster* showed increased production of recombinant offspring in response to two bacteria and to a parasitic

was, and this increase was driven by transmission distortion of recombinant chromatids – either during meiosis or due to asymmetric viability of gametes [76].

### **3) Molecular mechanisms governing variation in recombination rate**

Meiosis evolved in the early history of Eukaryotes, and many of the core mechanisms governing meiosis are highly conserved across the group [45, 99, 100]. Recombination is initiated by a DSB generated by SPO11 endonuclease, which is a DNA binding domain [see 101]. Most DSBs are repaired via a non-crossover (NCO) pathway, which results in gene conversion rather than the exchange of DNA between chromosomes (e.g. only 5 % of DSBs are repaired by CO in *Arabidopsis* [26]; ~10% in mice [102], ~60% in yeast [103]). Recombination is therefore a function of DSB formation, but also processes that govern CO versus NCO. Multiple factors govern the position of the DSB at multiple genomic scales; from the chromosome/sub-chromosomal regions to variation in the DNA sequence. DSBs occur predominantly within the euchromatic regions of the chromosome, preferentially in the chromatin loops, and are associated with several sequence features, with these mechanisms working hierarchically [see 99, 100]. For example, two identical DNA sequences can experience markedly different recombination frequencies if they occur within different chromatic regions [100]; likewise, an active initiation site can lose its activity if it is inserted into a region with low DSB activity [104]. In this section, we review the genetic and epigenetic factors that are associated with variation in recombination, reflecting this hierarchy; starting at the broad genomic scale, moving to DNA sequence and epigenetic levels.

#### **3a) How does genomic architecture relate to recombination?**

Genome-wide recombination rate has often been attributed to variation in the underlying genomic architecture, namely genome size, haploid chromosome number (HCN), changes in ploidy, chromosome size and chromosomal rearrangements. Although a negative relationship between genome size and recombination rate is often assumed, there is little robust data in support of this (see Box 2). Our analysis of linkage map data across Eukaryotes suggests little evidence that recombination rate decreases with genome size in Fungi and Animals, but that larger Plant genomes have reduced recombination rates (Figure 3a, Box 2). It should be noted that our data averages across genomes with different

chromosome numbers and across hetero- and euchromatic regions. In addition, we did not include data on the proportion of the genome that is heterochromatic, however we did explore the relationship between HCN and recombination rate. Although HCN explains variation in the total number of recombination events across a genome, i.e. the linkage map length (Figure 3b) it explains little variation in recombination rate per megabase (cM/Mb) (Figure 3c). Our analysis suggests that genome architecture may play a limited role in driving variation in recombination rate at a broad scale (after controlling for phylogeny), which is consistent with the prediction that changing the number of COs per chromosomes is more effective at changing the efficacy of selection compared to changing the number of chromosomes [105].

Considering variation between chromosomes, recombination can be absent or greatly reduced on entire chromosomes (i.e. absent in one sex (achiasmate) or on certain autosomes (e.g. *D. melanogaster* Chr 4 and *Toxoplasmodia gondii* Ch1a [106]), but also influenced by the presence of chromosomal rearrangements, such as inversions, fissions, fusions and translocations. Inversions represent a well-known case of rearrangement that can modify recombination: recombination is suppressed in individuals that are heterozygous for the inversion (heterokaryotype), because the inversion causes problems with pairing and segregation during meiosis [107]. This local suppression of recombination can also modify the recombination landscape in the longer term, so that suppression can extend to individuals homozygous for the inversion and to other, non-rearranged chromosomes [e.g. 20, 108, 109-111]. Such a long-term suppression of recombination due to strong selection may be achieved through a reduction in hotspot loci in the inverted and rearranged regions, which persists beyond the heterozygous state of such rearrangements [108].

One broad-scale and general pattern observed within chromosomes is a lower recombination rate around centromeres. While this could be attributed to selection against recombination in highly repetitive regions, repeat sequence is not necessary for suppression; organisms that have no or few centromeric repeats also show suppressed recombination at the centromere [112]. Suppression is likely driven by chromatin structure; DSB are less common in condensed heterochromatin, and chromatin environment can influence the probability that a DSB is repaired with a NCO rather than a CO [99]. Recently,

Talbert and Henikoff [112] argued that DSB and repair via NCO may be common in centromeres, and this could explain the accumulation of repetitive elements and diversification of centromeres, despite apparently little CO recombination. Differences in the chromatin structure between males and females may also explain sex differences in GwRR in mammals, for example in mice females have longer bivalents (less compact chromatin) and have greater CO number [113]. Although heterochromatic regions are often difficult to sequence and study, it is likely they can provide important insights into factors influencing CO and NCO repair mechanisms and recombination.

### **3b) Fine-scale molecular genetic mechanisms related to determining recombination**

The genome architecture and chromatin structure clearly influence large scale patterns in recombination, but what do we know about the patterns at smaller genomic scales? Recombination frequency and position co-vary consistently with several DNA sequence features; it is positively correlated with GC content and gene density and negatively correlated with Transposable Element (TE) density, and it is also consistently related to a number of gene regulatory elements and to histone modification (i.e. methylation) [for review, see 41, 99, 114, 115]. Determining cause and effect from these correlations is problematic [see 114 for discussion about TEs]. For example, recombination may drive increases in GC content via biased gene conversion in DSB repair in for example mammals [116], insects [117], birds [118] and rice [119]. However, in yeast, AT to GC substitutions are not directly correlated with recombination [120] and GC content may be a modifier of recombination [121]. Within genic regions, DSBs and subsequent recombination are more common in gene promoters or in regions with promoter-like features [see 26, 45, 99, 101].

In mammals and plants, several specific genetic mechanisms underlying variation in recombination rate have been identified. Loci that have been repeatedly implicated in this variation include *RNF212* (and its paralogue *RNF212B*), meiotic recombination protein *REC8*, and E3 ubiquitin-protein ligase *CCNB1IP1* homolog *HEI10*, which have been consistently associated with rate in maize, yeast, *Arabidopsis*, cattle, humans, mice and sheep [16, 18, 60, 77, 122-124]. Research in mice has shown that *RNF212* is essential for crossing-over, with a key role in synapsis and the formation of recombination complexes specific to COs [125], whereas *HEI10* plays an antagonistic role which is essential for regulating NCO/CO

processes [122]; studies suggest that these proteins have a dosage dependent effect on crossover rates.

As most recombination occurs in hotspots, understanding what governs hotspot position is highly relevant to revealing the genetic mechanisms governing recombination. The post-translational modification of histones, in particular trimethylation of lysine 4 on histone 3 (H3K4me3), is associated with DSB in many species [26, 67, 99, 101, 126]. The regulatory element PR domain zinc finger protein 9 (PRDM9), which can modify H3K4, has been shown to drive DSB formation in mice and humans [17]. Not all H3K4me3 sites are recombination hotspots and many species lack functional copies or orthologues of PRDM9 (e.g. *Drosophila*, yeast, dogs, birds and most plants), demonstrating that other mechanisms most certainly exist. In *Arabidopsis*, DNA methylation of H3K9me2 can suppress euchromatic CO hotspots [127]. There are likely to be at least two classes of hotspots; ancestral – occur in a wide range of organisms, are temporally stable and associated with gene promoter regions - and derived – location determined by e.g. the PRDM9 DNA binding motif and rapidly evolving [128]. Not all species studied have obvious recombination hotspots and considerable progress has also been made in determining the mechanisms governing recombination in these cases and outside hotspots. In *C. elegans* histone modifications do not strongly associate with recombination [129], however other post-translational modifications have been identified; phosphorylation of REC-1 has been shown to govern CO distribution in *C. elegans* [130].

#### **4) Evolutionary processes governing variation in recombination rate**

Recombination frequency is a heritable trait, which can be controlled by a few genes (oligogenic) [e.g. 16, 18, 43, 131] and/or by many genes (polygenic) [20, 98], and it can respond to selection [21, 22, 132]. Selection on recombination can be direct and indirect: it can act directly on variation in recombination when recombination influences gamete viability or fitness (direct consequence in offspring), and indirectly when recombination alters haplotype frequencies and increases selection efficacy (variation-and-selection models) [6, 133, 134]. With a growing understanding of the genes and molecular mechanisms determining variation in recombination frequency and landscape, and data accumulating in a greater range of organisms, we are in a good position to begin to address

long standing questions about how recombination evolves and how variation in recombination frequency or landscape influences evolutionary processes such as adaptation and speciation. In this section, we begin by exploring the evidence for indirect and direct selection on genome-wide recombination, we then discuss how selection acts to modify recombination in specific regions of the genome and how this influences local adaptation and speciation, and finish with discussion of the evolutionary explanations of the evolution of sex differences in recombination rate.

#### **4a) Indirect selection on variation in genome-wide recombination rate**

Indirect selection on recombination rate has received much empirical and theoretical consideration in order to understand the evolution of sex, but there has been less focus on understanding the processes that govern recombination variation in obligate sexuals [see 134]. Models of the evolution of sex suggest that one of the main advantages of recombination is that it can increase the efficacy of selection and facilitate adaptation [see 3, 105, 135, 136]. It does this by reducing the amount that genetic variants or alleles interfere with each other's response to selection. Alleles can interfere in at least two ways: first, when the presence of one allele alters the fitness effects of another allele (epistasis); and second, when the probability of two alleles at two different loci occurring together in a population is non-random (referred to as linkage disequilibrium (LD)), which can be due to their physical proximity on a chromosome (genetically linked) or because of selection, migration or drift [see 137]. For simplicity, we will use the more general term *allelic non-independence* to refer to LD, epistasis and other processes that make alleles behave non-independently. Allelic *non-independence* can interfere with how an allele responds to selection. For example, selection at one locus interferes with selection at other selected loci, reducing its probability of fixation (termed the Hill-Robertson interference (HRI) [136] and the degree of interference increases with genetic linkage between the loci under selection. Another example is when alleles in LD experience conflicting selection pressures - if a beneficial allele is associated with a deleterious allele it can be lost from the population, whereas a deleterious allele can rise to high frequency if it is associated with a beneficial allele. Finally, selection at one locus can reduce the level of polymorphism at linked loci (an effect called background selection when purifying selection acts on a deleterious allele and selective sweep when positive selection acts on a beneficial allele) and this selection at

linked sites was found to be a key factor determining genetic diversity within a species and diversity within the genome across animals and plants [138]. The most recognised benefits of recombination in sexual species is that it can increase the efficacy of selection by modifying the degree of independence among alleles: it can break down negative linkage disequilibrium generated by selection and drift, thus reducing HRI, it can create beneficial combinations of alleles and create greater genetic variation that selection can act on. What makes recombination paradoxical is that it can break apart combinations of beneficial alleles that selection has brought together, resulting in negative fitness effects, both direct [2] and indirect [4, 40]. Therefore, the benefits of recombination are dependent on how alleles are associated and how breaking up these associations influences fitness.

Several demographic and ecological factors can increase the number and strength of allelic non-independence within a population. For example, small effective population size ( $N_e$ ) and high rates of inbreeding or selfing will increase associations between alleles and thus HRI; in these cases, indirect selection should favour an increase in the rate of recombination [105, 139]. In line with this expectation, studies have found a negative association between recombination rate and indirect measures of  $N_e$  across species of animals and plants. In mammals, chiasma frequency per bivalent (Cf/B) was positively correlated with age at maturity, with greater age a proxy for smaller  $N_e$  [140] and in snails, it was negatively correlated with population density [54]. In plants, recombination (cM/Mb) was higher in large, long-lived tree species compared to shrubs and herbs [39], Cf/B was higher in selfing plants [141] and higher in annual plants that are likely experiencing higher rates of inbreeding and drift [50]. Higher rates of asexual reproduction, for example in parthenogenetic animals or fungi would also increase HRI and should also select for higher rates of recombination. In line with this prediction, we observed elevated recombination in parthenogenic animals compared to animals with gonochorus sexual systems - where all individuals are either male or female and reproduce sexually every generation (electronic supplementary material, Figure S4). Taken together these data suggest that optimal rates of recombination between species have evolved to reduce HRI and increase genetic variation and the efficacy of selection, however these relationships do not provide definitive proof of causality. For example, in mammals longer lived species have a longer meiotic arrest in females, which may favour higher recombination to prevent aneuploidy [142].



457

458 Increased recombination can also evolve in populations experiencing strong directional  
459 selection and drift [136], even when traits unrelated to meiosis or recombination are being  
460 selected for [e.g. 143, 144]. This may explain observations of increased recombination in  
461 some domesticated species [140, 145]. However, there is mixed evidence for changes in  
462 overall recombination rates between artificially selected populations and their wild  
463 progenitors [136]: a study comparing chiasma counts in wild and domesticated mammal  
464 species pairs saw no differences [146], suggesting that an increase in recombination is not a  
465 universal feature of domestication.

466

467 Populations experiencing heterogeneity in selection are also expected to benefit from  
468 higher rates of recombination. In particular, higher rates are predicted when organisms  
469 experience rapid oscillations in the fitness of certain allelic combinations, for example in  
470 organisms involved in a co-evolutionary arms race [1], or that experience fluctuating  
471 environments [5, 147] or inter-locus sexual conflict [148]. In an arms race scenario,  
472 parasite-induced selection on the host can drive increased recombination rate. This has  
473 been confirmed in several experimental evolution studies (See section 1e) and supported by  
474 indirect evidence: high recombination in genomic regions harbouring genes related to  
475 immunity (e.g. MHC [149], *Arabidopsis* [150]) and high somatic recombination observed in  
476 developing lymphocytes in jawed vertebrates [151]. Studies testing this model normally  
477 consider parasite-induced changes in the host; however, it is possible that host-induced  
478 selection on the parasite can also drive high recombination rate in parasites [152]. We  
479 tested this hypothesis with our data by comparing GwRR of parasitic or pathogenic species  
480 with free-living species. Using phylogenetic generalized linear models, we found parasitic or  
481 pathogenic species had a higher recombination rate compared to their free-living  
482 counterparts in SAR and in Animals, but there was no difference between parasitic or  
483 pathogenic and free living species of Fungi (electronic supplementary material Figure S5;  
484 Plants were excluded as data was not available for any parasitic or pathogenic plant  
485 species). Interestingly, parasites often have smaller genomes compared to their free-living  
486 counterparts, which is consistent with high recombination driving genome contraction  
487 (discussed earlier in Box 2), although genome contraction may also be due to selection on  
488 small cell size and fast replication rates [153, 154].

Spatial and temporal variation in the abiotic environment can also favour higher recombination [5, 137, 147], although there is little evidence testing this hypothesis in sexual species (studies more often compare between sexual and asexual populations). Temporal variation is often considered less likely to drive increases in recombination because the fluctuations in the abiotic environment are not fast or predictable enough [see 148]. Data collected in the field investigating the effects of spatial variation in abiotic environment on recombination often cannot rule out other confounding effects such as demography or biotic factors. For example, marginal populations of *Drosophila robusta*, which can experience greater environmental fluctuations, have fewer inversion heterozygotes and thus higher recombination rates [see 5]. In plants, higher Cf/B was found in annuals that are well suited to colonising new variable habitats [50]. However, in both cases recombination rate may be favoured because of the small  $N_e$  of marginal or colonising populations. More empirical work is needed to test this hypothesis, ideally comparing across natural populations while controlling for potential confounding effects.

Theoretically, differential selection pressure on males and females can induce fluctuating selection on an allele as it cycles through the male and female genomes [148]. Differential selection on male and female traits, such as mating rate or parental investment, creates intra-locus sexual conflict that could favour increased recombination [148]. One prediction that can be drawn from this model is that hermaphrodites, that do not have separate sexes and thus have low levels of intra-locus sexual conflict, should have lower recombination rates compared to species with separate sexes. We tested this in our data looking at how sexual system (gonochorous, hermaphrodite, male-haploid and parthenogenic) was related to recombination rate (GwRR/HCN) across animals. We found that parthenogenic and male haploid species had higher recombination rate compared to species with separate sexes, but found no difference between separate sexes and hermaphrodites (electronic supplementary material). The dataset used here has a limited number of hermaphrodites ( $n=7$ ) and it will be interesting to explore this question and other questions relating to the strength of sexual selection with more data.

#### **4b) Direct selection on variation in genome-wide recombination rate**

Considering direct selection on recombination, ensuring proper chromosome segregation and efficient DNA repair imposes stabilizing selection on recombination, thus creating an “optimal range” for a given organism. Extremely high or low rates of recombination outside this optimal range can have negative effects on fitness, for example, in humans and mice very low recombination rates can cause chromosomal abnormalities in gametes and reduce fertility, and very high rates can cause genomic instability and disease [155]. As discussed, obligate crossover requirements and genomic architecture can explain some, but not all, of the variation observed between species in the optimal range of GwRR (Box 2). Changes in the environment can push recombination beyond the optimal range with negative fitness consequences, and tolerance to these perturbations may explain some of the variation between species [90].

Considering less extreme modifications of recombination (within the optimal range), there are few studies linking genome-wide recombination rate to fitness, but there is no clear directional pattern. In populations at equilibrium, recombination is expected to reduce fitness because it breaks apart allelic combinations that selection has favoured (termed recombination load) [2] and several studies in *Drosophila* support this prediction [e.g. 2, 156, 157]. In humans, a positive relationship between GwRR (cM/Mb) and female fecundity was found, which was argued to be due to a higher number of COs reducing the frequency of age-related non-disjunction, and increasing the likelihood that the gamete became a live birth (realised recombination) [131]. In flour beetles (*T. castaneum*), lines that evolved longer linkage map lengths (i.e. higher GwRR) during coevolution with their parasite were found to have higher fitness in the absence of the parasite compared to lines with shorter linkage maps [98]. The authors did not identify any possible explanations, but posited that it may be due to co-evolution with the parasite selecting for fitter beetles. Although studies at the genome-wide level provide evidence of correlations, they may not be very informative with respect to the mechanisms underlying any fitness-recombination relationships. Studies that can quantify where in the genome recombination is modified, not just the change in overall rate, are likely to provide more insight into the traits that are involved and how changes in recombination influence these.

#### **4c) Selection on recombination rate modification in regions of the genome**

In comparison to the genome-wide scale, there is good evidence that selection acts to reduce recombination on specific chromosomes (i.e. sex chromosomes) and smaller regions of the genome capturing co-adapted loci, quantitative trait loci (QTLs) and reproductive isolating loci (i.e. inversions, supergenes). Recombination between these sets of co-adapted loci can negatively affect offspring fitness and adaptation, and strong selection against recombination in these regions is expected to outweigh relatively weak selection for increased recombination to reduce HRI (Lenormand and Otto 2000). Processes leading to tight physical linkage can reduce effective recombination between sets of adaptive and reproductive isolating loci, therefore playing a key role in adaptation and speciation [8, 158], and can be selected for under prolonged periods of gene flow between locally adapted or diverging populations [107, 137, 159]. Regions of tight linkage can evolve as a consequence of several, non-exclusive mechanisms including: genomic rearrangements (translocations, inversions, transposable elements or duplications (Yeaman 2013, Ortiz-Barrientos et al. 2016)), supergenes, (i.e. a group of tightly linked loci that regulate a phenotype [160]) and an establishment bias where linkage with an already diverged locus can favour the establishment of new advantageous mutations nearby [159, 161]. An increasing number of empirical studies find evidence for concentrated regions of adaptive and reproductive isolating loci (supergenes, tight linkage) or their presence in regions of reduced recombination (e.g. sex chromosomes, inversions), as well as evidence for a negative correlation between recombination rate and genetic differentiation (see Table 2, provides a non-exhaustive list of recent examples).

#### **4d) Evolutionary explanations for sex differences in recombination**

The prevailing hypothesis for the complete absence of recombination in the heterogametic sex is that achiasmy is a pleiotropic effect of selection for tight linkage on the Y or W chromosomes and/or suppression of recombination between the heterogametic sex chromosomes [73, 75]. However, reduced recombination is not always observed in the heterogametic sex (i.e. birds and moths) and it cannot explain variation between the sexes in hermaphrodites [162]. Understanding the conditions under which heterochiasmy evolves has been the subject of extensive theoretical attention and debate [e.g. 75], but as yet, there is no consensus on its evolutionary drivers. Arguments related to the relative strengths of sexual selection, sperm competition and dispersal remain weakly supported by

empirical data [163], with some arguing that sex differences are primarily driven by drift [73, 75]. Nevertheless, there are two arguments gaining broader theoretical and empirical support. The first is haploid selection; the sex experiencing the strongest haploid selection should recombine less (see Lenormand 2005). In plants, both female and male gametes have a haploid phase, but Lenormand (2005) proposed that selfing could be used a proxy for the strength of selection on the female haploid phase, and showed that the degree of heterochiasmy (male-female ratio) was higher in species with moderate to high selfing. The second is the role of meiotic drive, for example where asymmetry in female meiosis can be exploited by selfish genetic elements associated with centromere strength [69, 164, 165]; selection for increased recombination at centromeric regions will counteract drive by increasing the uncertainty of segregation into the egg [164].

## **5) Concluding remarks and future directions**

Recombination is a fundamental component of meiosis and a near universal mechanism in multi-cellular organisms, with far reaching effects on an individual's fitness and on evolutionary processes. Whole genome sequencing, dense marker panels and the development of new approaches to estimate population-scaled recombination rates have provided new opportunities to estimate recombination at much greater resolution and across natural populations, with great impact. Genome-wide averages of recombination rate are useful for broad-scale comparisons; however, averaging the number of recombination events across the genome can mask the dynamic nature of changes in distribution at a finer genomic scale. Studies in the future should consider the fine genomic landscape and not only the frequency. Across Eukaryotes there is large variation between taxa, populations and individuals in the frequency and distribution of recombination. In Figure 1 we illustrate how variation collected and compared across different taxonomic scales provides complementary information to address many important and outstanding questions about how and why recombination varies.

Significant progress has been made recently in identifying the genetic and epigenetic mechanisms governing the recombination landscape, for example, the presence or absence of one locus in particular (*PRDM9*) can explain variation across species in how conserved or dynamic their recombination landscape is. However, it is unclear how widespread

recombination hotspots are, and if all hotspots fall broadly into two categories - conserved versus rapidly evolving, although comparative studies are moving some way to elucidate this issue [67]. Other features of the recombination landscape, such as sex differences and plasticity, are also lacking empirical support across a wide range of taxa. We urge researchers to collect recombination data at the fine genomic scale in a greater range of species, in particular neglected taxa (marine microorganisms, basal animals and plants) and to estimate (and report) both sex-specific and sex averaged recombination rates. LD-based estimates are likely to be especially powerful in this respect as they provide opportunities to estimate recombination rate from polymorphism data of sampled populations without the need to create crosses or use pedigrees. Data from a greater range of species can further our understanding of the molecular mechanisms underlying recombination and enable us to address a range of long standing questions regarding the evolution of recombination.

Understanding the fitness consequences and evolutionary processes driving variation in recombination rate is still in its infancy. Investigation of how changes in recombination can directly influence phenotypic traits and fitness is needed and, although established theory on the evolution of sex considers the conditions under which changes in genome-wide recombination rate may be favoured, there is little empirical data testing these predictions in sexual organisms. More comparisons across related taxa, populations and individuals in the field are needed to characterise natural variation in recombination rate. Comparisons across populations and taxa could ask if, for example, drift, fluctuating selection and modes of reproduction co-vary with variation in recombination. Studying the recombination landscape across an environmental or ecological gradient while controlling for possible confounding effects of drift and changes in  $N_e$  are likely to be most informative. Experimental evolution studies could manipulate population parameters and see if recombination rate evolves in response to changes in density, inbreeding, fluctuating selection and parasites, and could investigate how changes in recombination rate influence fitness related traits.

More effort should be devoted to modelling recombination rate as a quantitative trait and consider how it will respond to different selection regimes in sexually reproducing organisms [see 134]. Models of the evolution of genome-wide recombination rates may

649 have limited explanatory power to explain variation in the landscape at fine genomic scales.  
650 Mathematical models could explore how selection influences patterns of recombination  
651 near loci under strong selection or loci involved in coevolutionary arms races, for example.  
652 Regional suppression of recombination on specific genomic features (inversions,  
653 supergenes) is receiving increased attention in the literature, spurred on by the recognition  
654 that the association of these features with suppressed recombination is key to adaptation  
655 and speciation in the presence of gene flow. Current empirical challenges reside in  
656 determining the sequence of events that have permitted favourable genomic features or  
657 recombination modifiers to establish and be maintained in the presence of gene flow, from  
658 the selection of pre-existing favourable genomic features to the selection of mechanisms  
659 generating them during the course of the processes of adaptation and speciation.

660  
661 To summarise, there is enormous variation in recombination frequency and landscape  
662 across species and genomes. Great progress has been made in determining the genetic and  
663 epigenetic factors controlling recombination, but more theoretical and empirical data are  
664 needed to further our understanding of why recombination varies and to determine if this  
665 variation is the result of selection.

### **Box 1. Estimating recombination rate**

Two parameters can describe how patterns of recombination vary between any two individuals or groups of individuals: the genome-wide recombination rate (how often COs occur e.g. in a given meiosis) and the recombination landscape (where COs occur in the genome). These estimates of recombination rate are commonly expressed as recombination frequency per mega- or kilobase per generation [11, 33, 34, 39-41] and can be estimated at different genomic resolutions. Historically, recombination rates were estimated by directly counting the number of chiasmata during meiosis using cytogenetic methods, and from early linkage maps, where phenotypes and/or genetic markers were ordered along chromosomes based on the frequency at which they were co-inherited (i.e. not separated by a crossover). A spacing of one centimorgan (cM) indicates a one percent chance that two genes will be separated by crossing over. Both approaches provided coarse-scale estimates of recombination frequency, but lacked accuracy. In particular, linkage map estimates of recombination require pedigree information and are limited by the number of independent meioses characterised (i.e as a function of sample size, pedigree size and depth) and if marker densities are low they fail to capture all COs and underestimate map length [166, 167]. Low-resolution estimates of recombination provide limited information about the recombination landscape, but can provide useful data for looking at large-scale differences between chromosomes, chromosome arms or chromosome segments. These estimates also provide common measures that are comparable across larger taxonomic scales.

Today, the resolution to determine recombination rates and landscapes has dramatically improved with developments in high-throughput sequencing and genotyping technologies. It is now feasible to obtain estimates of recombination rate on a finer genomic scale, with dense linkage maps and population-scaled estimates of recombination rate. Whilst linkage maps provide an estimate of crossovers observed over a few generations, population-scaled approaches provide estimates of historical recombination [168]. This approach uses high-density marker and/or genome sequence data to estimate population-scaled recombination rates ( $\rho$ ) using coalescent methods that model patterns of linkage disequilibrium, the non-random association of alleles across loci, within narrow genomic regions. These approaches have been used to identify recombination “hotspots”. A limitation of coalescent estimates is that linkage disequilibrium is also affected by the effective population size of a population,



which is influenced by the population's demographic history (e.g. bottlenecks, gene-flow, selection [e.g. 169]). However, new developments in population-based approaches are implementing ways to account for demographic history during recombination rate inference [e.g. 64, 170].

Despite their differences, results from linkage map and population-based estimates are highly correlated [58, 65, 78, 169, 171]. It is also important to note that all marker based estimates (linkage maps and population based estimates) can only detect a recombination event that results in a change in the allelic combination in the next generation (effective recombination) – for example, if parents are homozygote across many markers the action of recombination is not detectable, and recombination is typically only measured from gametes that successfully produced offspring (realised recombination). One method to quantify recombination events in all gametes, not just those that produce offspring, is to genotype or whole genome sequence single sperm. For example, in humans this approach has been used to fine-map the recombination landscape and investigate transmission distortion and allelic drive [172], and in *Daphnia* it was used to build a genetic linkage that helped to improve the genome assembly [173].

## **Box 2. How does recombination rate vary with genome architecture?**

### **Genome size**

Following the observation that linkage map length was similar across Eukaryotes despite large variation in genome size, it was proposed that larger genomes have several orders of magnitude lower recombination rates [36]. This is consistent with the observed relationships between recombination rate and sequence features; recombination rate is positively correlated with gene density and negatively with the density of repetitive elements, which could drive lower recombination rates in large, repeat-rich genomes [41, 114]. Higher recombination rate can also lead to reductions in genome size - if recombination rate increases mutation rate and small deletions are more common than small insertions (mutational bias), purifying selection on these mutations can drive genome contraction [153, 174]. Both positive and negative relationships between genome size and recombination rate have been found (positive [44], negative [34, 35, 41]). The disparity in results may be attributed to differences in the methods used and taxonomic breadths considered, but may also be due to statistical problems. When recombination rate is calculated as the linkage map length (cM) divided by genome size (Kb or Mb), then genome size and recombination are mathematically coupled; it is not appropriate to test for relationship between mathematically coupled variables [175]. To investigate the relationship between genome size and recombination rate, we examined the fit of linear and quadratic relationships between linkage map length and genome size, while controlling for phylogeny. In Animals and Fungi, a linear model best fit the data, but in Plants, a quadratic model was a better fit (see Figure 3a and electronic supplementary material). This suggests that recombination rate is lower in larger Plant genomes, but in Animals and Fungi there is no evidence to suggest recombination rate declines with genome size.

### **Haploid chromosome number**

The number and size of chromosomes can explain variation in GwRR because a minimum of one CO per chromosome (or chromosome arm) is often required to ensure proper segregation of chromosomes during meiosis [13, 43, 134, 176, 177]. There are several exceptions (e.g. achiasmate species; see section 1d) and often more than one CO per chromosome is observed on larger chromosomes [see 177]. Under the obligate CO requirement, higher recombination rate could be achieved by increasing the number of

chromosomes or by having smaller chromosomes, with bird genomes, containing many microchromosomes, providing support for this hypothesis [171, 178]. Whether karyotypic variation is driven by selection on recombination rate is unclear [e.g. 47, 179], but Burt [105] demonstrated that an increase in the efficacy of selection was better achieved by increasing the number of crossovers per chromosome rather than increasing the number of chromosomes. Whole genome duplication and polyploidy are dramatic ways to increase chromosome number, and under an obligate CO requirement this should result in at least a doubling of chiasma frequency. Polyploids' ability to achieve stable meiosis may be partly due to a reduction in GwRR (and increase in interference distance) to ensure only one CO per pair of homologous chromosomes, as a mechanism to avoid the pairing of three or more homologous chromosomes [180, 181]. The data we compiled provide an opportunity to test if haploid chromosome number (HCN) explains variation in linkage map length and GwRR (cM/Mb) across Eukaryotes. A positive linear relationship between linkage map length and HCN was found for Plants and Fungi, while in Animals a quadratic relationship was slightly better at explaining this relationship (Figure 3b, electronic supplementary material). We found the HCN was not related to GwRR (per megabase) in Fungi and Animals, and although a relationship was found in Plants, the amount of variation explained was low ( $r^2 = 0.02$ ) (see Figure 3c and electronic supplementary material). Despite explaining little variation, we do suggest that scaling GwRR by haploid chromosome number provides a useful comparative measure of recombination rate and removes variation attributable to the obligate crossover requirement.

## Acknowledgements

We are grateful to Roger Butlin for suggesting we prepare the special issue, and to Helen Eaton and two anonymous reviewers for their comments on the MS. JS is supported by a fellowship from ACE, ETH Zürich. PGDF is supported by funding from the Swiss National Science Foundation (SNSF proposal numbers 31003A\_163446 and 310030E-160812). CMS acknowledges support from the Agence Nationale pour la Recherche and the CNRS, France. SEJ is supported by a Royal Society University Research Fellowship. This is publication ISEM 2017-XXX.



779 **Table 1.** Summary of the linkage map data compiled from the literature; linkage map length  
780 (centimorgans, cM), Genome size (Megabases, Mb), haploid chromosome number and  
781 recombination rate (cM/Mb).  
782

Group	Linkage Map Length (cM)				Genome Size (Mb)			Haploid Chromosome Number			Recombination Rate (cM/Mb)		
	n	mean	min	max	mean	min	max	mean	min	max	mean	min	max
SAR	9	1782	653	2884	189	18.87	560	18.78	9	34	38.67	3.24	108.00
Fungi	15	2068	86	5860	49.26	19.05	170.2	13.27	4	21	48.68	1.40	119.90
Animals	140	1813	90	5961	1538	43.15	30880	22.27	3	73	2.52	0.12	28.10
Plants	189	1567	309	8184	2956	120.40	29280	13.91	5	90	1.85	0.03	9.22
Total or Mean	353	1807.5			1183.0			17.05			22.93		

783  
784

785 **Table 2.** Summary of selected studies demonstrating a link between regional suppression of recombination and adaptation and/or speciation.  
786 Details include study species, the main finding and the methods used to identify regions of suppressed recombination (CG=cytogenetic,  
787 LM=linkage mapping, LD=LD based estimate of recombination rate and Others). Studies are grouped according to nature of the relationship  
788 between recombination suppression and either adaptive and/or reproductive isolating (RI) traits or genetic differentiation.

789

<b>a) Adaptive and RI traits map to recombination coldspots</b>						
Study system	Main finding	CG	LM	LD	Other	Ref
<b>Inversion clines related to local adaptation</b>						
Fruit fly ( <i>Drosophila melanogaster</i> )	latitudinal cline in inversion, which has shifted with climate change				X	[182]
Mosquito ( <i>Anopheles gambiae</i> )	genetic differentiation pronounced at inversion breakpoints across an aridity cline	X				[183]
Seaweed fly ( <i>Coelopa frigida</i> )	demonstrating local adaptation of the inversion along a tidal cline	X				[184]
<b>Inversions capture adaptive and/or RI traits</b>						
Humans ( <i>Homo sapiens</i> )	inversion shows molecular signatures of positive selection and is associated with higher fitness				X	[185]
Butterfly ( <i>Heliconius numata</i> )	supergene for mimicry traits is associated with chromosomal rearrangements			X	X	[186]
Threespine stickleback ( <i>Gasterosteus aculeatus</i> )	elevated genetic differentiation and adaptive loci associated with inversions				X	[187]
Atlantic cod ( <i>Gadus morhua</i> )	putative inversion association with salinity tolerance			X		[188]
Monkey flower ( <i>Mimulus guttatus</i> )	inversion with adaptive QTLs is the most divergent region between annual and perennial ecotypes		X			[189]
European corn borer moth ( <i>Ostrinia nubilalis</i> )	inversion contributed to accumulation of ecologically adaptive alleles and genetic differentiation		X			[190]
Drummond's rockcress ( <i>Boechera stricta</i> )	inversions captured multiple adaptive QTLs for phenology	X	X	X		[191]
<b>Sex chromosomes</b>						
Threespine stickleback ( <i>G. aculeatus</i> )	loci for behavioural isolation and hybrid male sterility map to ancestral and neo X chromosome		X			[192]
House mouse ( <i>Mus musculus musculus</i> / <i>domesticus</i> )	recombination modifier (Hstx2/Meir1) and hybrid sterility locus (Hstx2) genetically linked on X	X				[193]

790

791

<b>b) Increased genetic differentiation (GD) in recombination coldspots</b>						
Study system	Main finding	CG	LM	LD	Other	Ref
<b>Involving chromosomal rearrangements</b>						
Mosquito ( <i>A. funestus</i> )	ecotypes segregate for inversion but GD is low outside the inversion	X				[194]
Apple maggot fly ( <i>Rhagoletis pomonella</i> )	regions inside and near an inversion had higher GD compared to collinear regions further away			X		[195]
Fruit fly ( <i>D. pseudoobscura</i> , <i>D. persimilis</i> )	pairwise GD higher in intergenic regions inside and near an inversion	X				[196]
House mouse ( <i>M. m. domesticus</i> )	increased GD in proximal regions of Robertsonian fusions	X				[197]
Monkey flower ( <i>M. guttatus</i> )	increased GD in inversions, evidence that inversion have been under recent selection		X			[198]
<b>Concentrated in or around centromeres</b>						
Mosquito ( <i>A. gambiae</i> )	elevated sequence divergence near centromeres				X	[199]
Princess cichlid fish ( <i>Neolamprologus savoryi</i> -complex)	introgression increased with distance from chromosome center				X	[200]
<b>Concentrated in or around sex chromosomes and/or centromeres</b>						
Rabbits ( <i>Oryctolagus cuniculus algirus</i> , <i>O. c. cuniculus</i> )	regions of high GD more common on sex chromosome and near centromeres				X	[201]
Mosquito ( <i>Anopheles</i> spp)	barriers to introgression on X chromosomes and low recombining pericentromeric regions			X	X	[202]

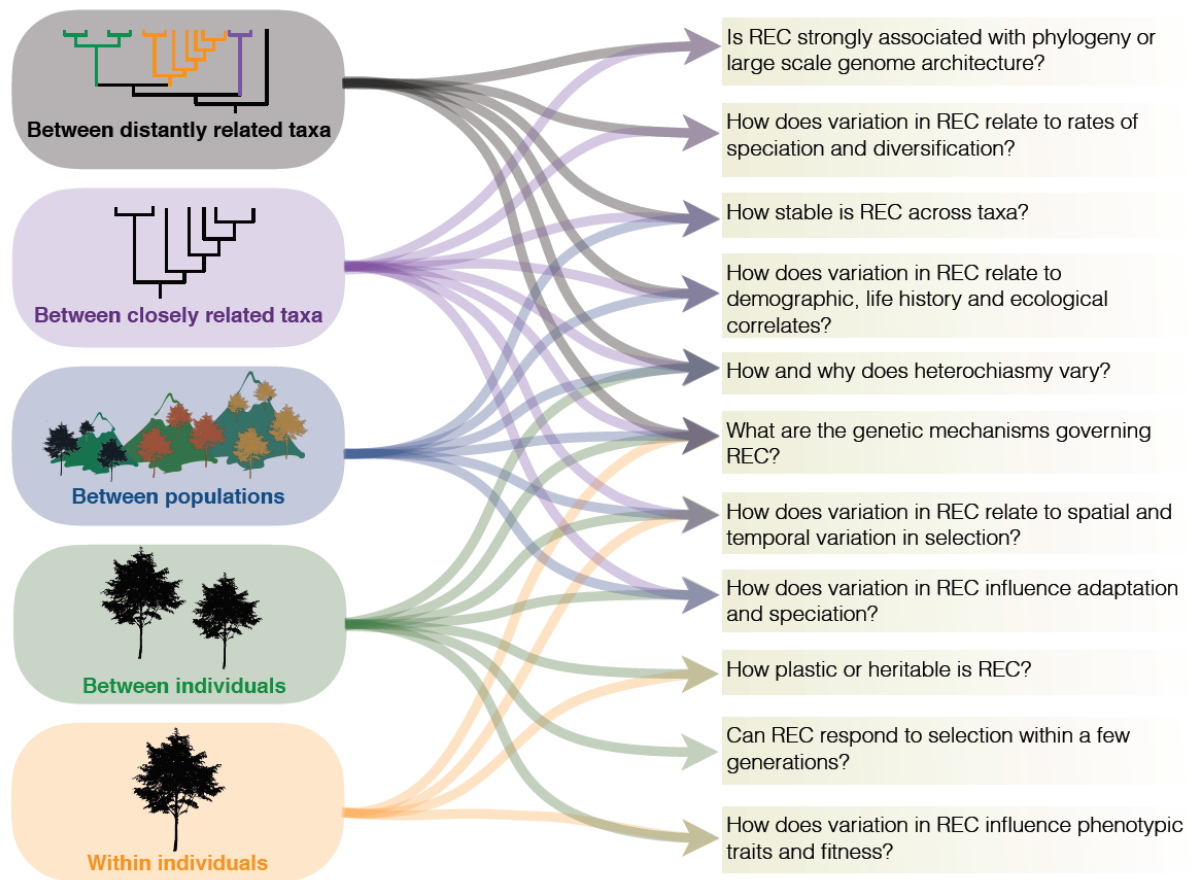
792

c) Genome-wide negative correlation of genetic differentiation and recombination rate						
Study system	Main finding	CG	LM	LD	Other	Ref
<b>Genomic differentiation estimated with SNPs from whole genome sequencing</b>						
Monkey flower ( <i>M. nasutus/guttatus</i> )	negative relationship between recombination rate and absolute divergence		X			[203]
Flycatchers ( <i>Ficedula albicollis</i> , <i>F. hypoleuca</i> , <i>F. speculigera</i> , <i>F. semitorquata</i> )	differentiation is explained by variation in recombination rate and the density of targets for selection		X			[204]
Threespine stickleback ( <i>G. aculeatus</i> )	recombination rates in regions of exceptional differentiation were often reduced			X		[205]
Crows ( <i>Corvus (corone) spp</i> )	heterogeneity in genetic differentiation is explained by linked selection on a shared genome architecture			X		[206]
European and American aspens ( <i>Populus tremula</i> , <i>P. tremuloides</i> )	linked selection generates heterogeneity of differentiation correlated with recombination			X		[207]
Darwin finches ( <i>Geospiza</i> , <i>Camarhynchus</i> , <i>Platyspiza</i> , <i>Pinaroloxias spp</i> )	genomic islands of locally elevated sequence divergence have low recombination rates			X		[208]
<b>Genomic differentiation based on SNPs from transcriptome sequence data</b>						
Sunflowers ( <i>Helianthus annuus</i> , <i>H. petiolaris</i> , <i>H. debilis</i> , <i>H. argophyllus</i> )	highly differentiated regions are associated with reduced recombination rates		X			[209]
House mouse ( <i>M. m. musculus</i> , <i>M. m. domesticus</i> , <i>M. m. castaneus</i> )	levels of differentiation were generally higher in regions of low recombination		X			[210]
<b>Genomic differentiation based on SNPs sampled using SNP-chip, reduced representation libraries</b>						
Humans ( <i>H. sapiens</i> )	F <sub>ST</sub> reduced in the portion of the genome with the highest recombination rate		X			[211]
Threespine stickleback ( <i>G. aculeatus</i> )	recombination rate correlates with the magnitude of allele frequency shift		X			[212]
House mouse ( <i>M. m. musculus</i> , <i>M. m. domesticus</i> )	reduced introgression and higher genomic differentiation associated with lower rates of recombination					[213]
Threespine stickleback ( <i>G. aculeatus</i> )	adaptive alleles occur more often in regions of low recombination in presence of divergent selection and gene flow		X			[214]

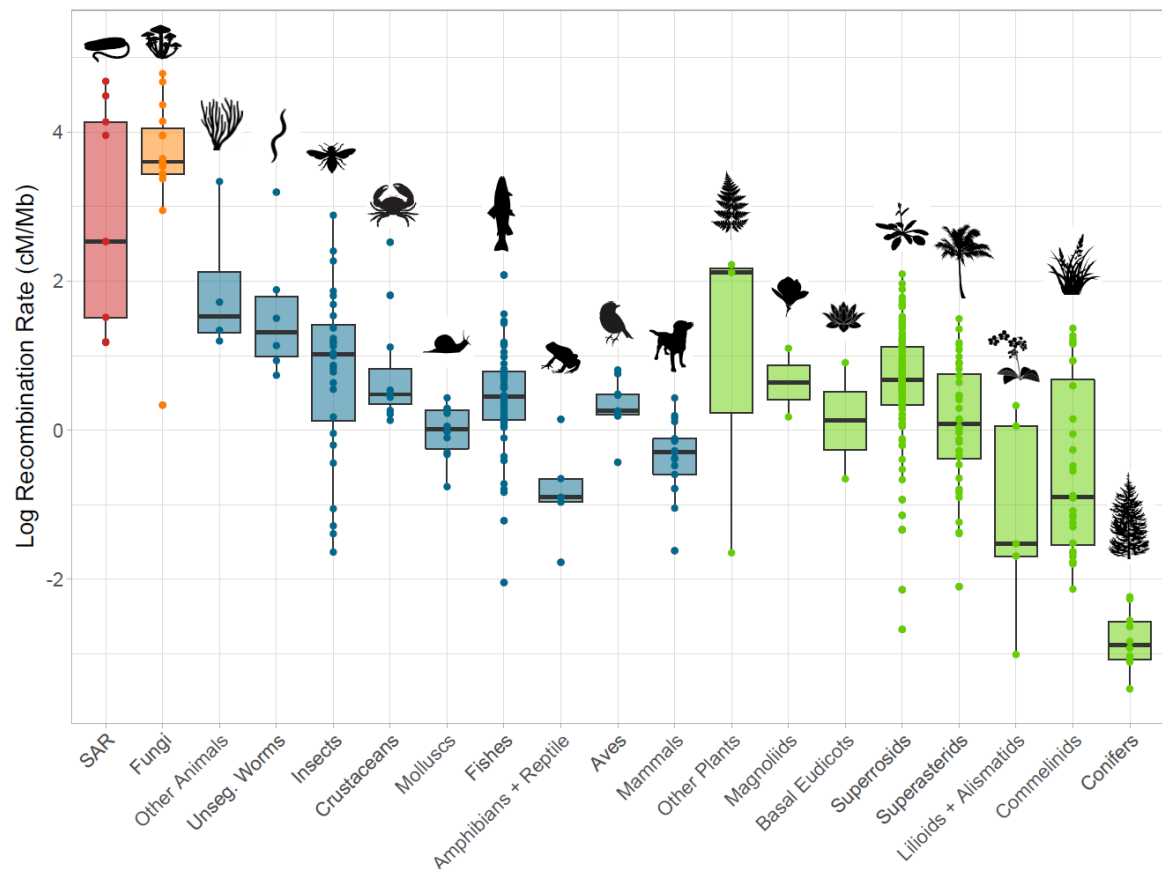
793

794

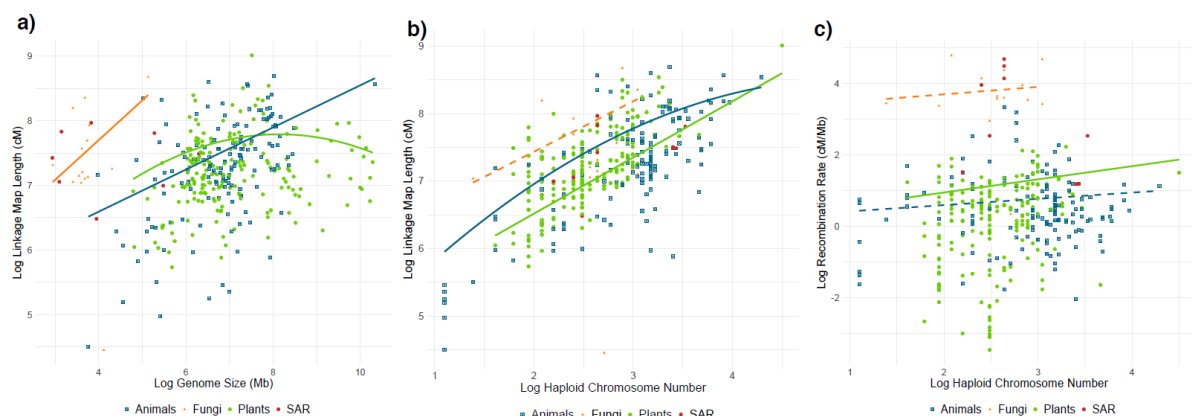




**Figure 1.** Comparing recombination landscape and frequency (REC) across different taxonomic and spatial scales (boxes on the left) provides complementary data to address outstanding questions about how and why recombination varies (boxes on right).



**Figure 2.** Variation in log of recombination rate, estimated by dividing linkage map length in centimorgans (cM) by genome size (Mb) across Eukaryotes taxa. Other plants: Pteridophyta, Chlorophyta, Bryophyta. Other Animals: Anthzoa, Holothuriodea, Ascidaceae.



**Figure 3.** Observed (points) and fitted (lines) relationships between a) Log genome size (Megabases, Mb) with log linkage map length (Centimorgans, cM), b) log haploid chromosome number with log linkage map length and c) log haploid chromosome number plotted against log recombination rate measured as linkage map (cM) length divided by

genome size (Mb). Fitted linear and quadratic relationships were obtained by fitting a phylogenetic generalized linear model separately for Plants, Animals and Fungi.

## References

- [1] Otto, SP. 2009 The evolutionary enigma of sex. *Am. Nat.* **174**, S1-S14.
- [2] Charlesworth, B & Barton, NH. 1996 Recombination load associated with selection for increased recombination. *Genetical Res.* **67**, 27-41.
- [3] Barton, NH. 1995 A general model for the evolution of recombination. *Genetical Res.* **65**, 123-144.
- [4] Rice, WR. 2002 Experimental tests of the adaptive significance of sexual recombination. *Nat. Rev. Genet.* **3**, 241-251.
- [5] Charlesworth, B. 1976 Recombination modification in a fluctuating environment. *Genet.* **83**, 181-195.
- [6] Otto, SP & Lenormand, T. 2002 Resolving the paradox of sex and recombination. *Nat. Rev. Genet.* **3**, 252-261.
- [7] Felsenstein, J. 1981 Skepticism towards santa rosalia, or why are there so few kinds of animals? *Evolution* **35**, 124-138.
- [8] Ortiz-Barrientos, D, Engelstädter, J & Rieseberg, LH. 2016 Recombination rate evolution and the origin of species. *Trends Ecol. Evol.* **31**, 226-236.
- [9] Fledel-Alon, A, Wilson, DJ, Broman, K, Wen, X, Ober, C, Coop, G & Przeworski, M. 2009 Broad-scale recombination patterns underlying proper disjunction in humans. *PLoS Genet.* **5**, e1000658.
- [10] Hassold, T & Hunt, P. 2001 To err (meiotically) is human: the genesis of human aneuploidy. *Nat. Rev. Genet.* **2**, 280-291.
- [11] Myers, S, Bottolo, L, Freeman, C, McVean, G & Donnelly, P. 2005 A fine-scale map of recombination rates and hotspots across the human genome. *Science* **310**, 321-324.
- [12] Hinch, AG, Tandon, A, Patterson, N, Song, YL, Rohland, N, Palmer, CD, Chen, GK, Wang, K, Buxbaum, SG, Akylbekova, EL, et al. 2011 The landscape of recombination in African Americans. *Nature* **476**, 170-175.
- [13] Coop, G & Przeworski, M. 2007 An evolutionary view of human recombination. *Nat. Rev. Genet.* **8**, 23-34.
- [14] Smukowski, CS & Noor, MAF. 2011 Recombination rate variation in closely related species. *Heredity* **107**, 496-508.
- [15] Bell, G. 1982 *The masterpeice of nature. The evolution and genetics of sexuality*. London, Coom Helm.
- [16] Johnston, SE, Berenos, C, Slate, J & Pemberton, JM. 2016 Conserved genetic architecture underlying individual recombination rate variation in a wild population of soay sheep (*Ovis aries*). *Genet.* **203**, 583-598.
- [17] Baudat, F, Buard, J, Grey, C, Fledel-Alon, A, Ober, C, Przeworski, M, Coop, G & de Massy, B. 2010 PRDM9 is a major determinant of meiotic recombination hotspots in humans and mice. *Science* **327**, 836-840.
- [18] Ma, L, O'Connell, JR, VanRaden, PM, Shen, BT, Padhi, A, Sun, CY, Bickhart, DM, Cole, JB, Null, DJ, Liu, GE, et al. 2015 Cattle sex-specific recombination and genetic control from a large pedigree analysis. *PLoS Genet.* **11**, e1005387.

856 [19] Dumont, BL, Broman, KW & Payseur, BA. 2009 Variation in genomic recombination  
857 rates among heterogeneous stock mice. *Genet.* **182**, 1345-1349.

858 [20] Hunter, CM, Huang, W, Mackay, TFC & Singh, ND. 2016 The genetic architecture of  
859 natural variation in recombination rate in *Drosophila melanogaster*. *PLoS Genet.* **12**,  
860 e1005951.

861 [21] Chinnici, JP. 1971 Modification of recombination frequency in *Drosophila*. I. Selection  
862 for increased and decreased crossing over. *Genet.* **69**, 71-83.

863 [22] Shaw, DD. 1972 Genetic and environmental components of chiasma control. 2. Response  
864 to selection in *Schistocerca* *Chromosoma* **37**, 297-308.

865 [23] Hillers, KJ. 2004 Crossover interference. *Curr. Biol.* **14**, R1036-R1037.

866 [24] Gerton, JL, DeRisi, J, Shroff, R, Lichten, M, Brown, PO & Petes, TD. 2000 Global mapping  
867 of meiotic recombination hotspots and coldspots in the yeast *Saccharomyces cerevisiae*.  
868 *Proc. Natl. Acad. Sci. U.S.A.* **97**, 11383-11390.

869 [25] Croll, D, Lendenmann, MH, Stewart, E & McDonald, BA. 2015 The impact of  
870 recombination hotspots on genome evolution of a fungal plant pathogen. *Genet.* **201**, 1213-  
871 1228.

872 [26] Choi, K & Henderson, IR. 2015 Meiotic recombination hotspots – a comparative view.  
873 *Plant J.* **83**, 52-61.

874 [27] Latrille, T, Duret, L & Lartillot, N. THIS ISSUE The Red-Queen model of recombination  
875 hot-spot evolution: a theoretical investigation. *Phil. Trans. R. Soc. B.*

876 [28] Singhal, S, Leffler, EM, Sannareddy, K, Turner, I, Venn, O, Hooper, DM, Strand, AI, Li, Q,  
877 Raney, B, Balakrishnan, CN, et al. 2015 Stable recombination hotspots in birds. *Science* **350**,  
878 928-932.

879 [29] Rockman, MV & Kruglyak, L. 2009 Recombinational landscape and population genomics  
880 of *Caenorhabditis elegans*. *PLoS Genet.* **5**, e1000419.

881 [30] Wallberg, A, Glémin, S & Webster, MT. 2015 Extreme recombination frequencies shape  
882 genome variation and evolution in the Honeybee, *Apis mellifera*. *PLoS Genet.* **11**, e1005189.

883 [31] Comerón, JM, Ratnappan, R & Bailin, S. 2012 The many landscapes of recombination in  
884 *Drosophila melanogaster*. *PLoS Genet.* **8**, e1002905.

885 [32] Smukowski Heil, CS, Ellison, C, Dubin, M & Noor, MAF. 2015 Recombining without  
886 hotspots: A comprehensive evolutionary portrait of recombination in two closely related  
887 species of *Drosophila*. *Genom. Biol. Evol.* **7**, 2829-2842.

888 [33] Wilfert, L, Gadau, J & Schmid-Hempel, P. 2007 Variation in genomic recombination  
889 rates among animal taxa and the case of social insects. *Heredity* **98**, 189-197.

890 [34] Lynch, M. 2006 The origins of eukaryotic gene structure. *Mol. Biol. Evol.* **23**, 450-468.

891 [35] Awadalla, P. 2003 The evolutionary genomics of pathogen recombination. *Nat. Rev.*  
892 *Genet.* **4**, 50-60.

893 [36] Thuriaux, P. 1977 Is recombination confined to structural genes on the eukaryotic  
894 genome? *Nature* **268**, 460-462.

895 [37] Orme, CDL, Freckleton, RP, Thomas, GH, Petzoldt, T, Fritz, SA & Isaac, NJB. 2013 *CAPER*:  
896 *comparative analyses of phylogenetics and evolution in R*. 145-151 p.

897 [38] Hinchliff, CE, Smith, SA, Allman, JF, Burleigh, JG, Chaudhary, R, Coghill, LM, Crandall, KA,  
898 Deng, J, Drew, BT, Gazis, R, et al. 2015 Synthesis of phylogeny and taxonomy into a  
899 comprehensive tree of life. *Proc. Natl. Acad. Sci. U.S.A.* **112**, 12764-12769.

900 [39] Jaramillo-Correa, JP, Verdú, M & González-Martínez, SC. 2010 The contribution of  
901 recombination to heterozygosity differs among plant evolutionary lineages and life-forms.  
902 *BMC Evol. Biol.* **10**, 22.

903 [40] Nachman, MW & Payseur, BA. 2012 Recombination rate variation and speciation:  
 904 theoretical predictions and empirical results from rabbits and mice. *Phil. Trans. R. Soc. B*  
 905 **367**, 409-421.

906 [41] Tiley, GP & Burleigh, G. 2015 The relationship of recombination rate, genome structure,  
 907 and patterns of molecular evolution across angiosperms. *BMC Evol. Biol.* **15**, 194.

908 [42] Gaut, BS, Wright, SI, Rizzon, C, Dvorak, J & Anderson, LK. 2007 Recombination: an  
 909 underappreciated factor in the evolution of plant genomes. *Nat. Rev. Genet.* **8**, 77-84.

910 [43] Dumont, BL. 2017 Variation and evolution of the meiotic requirement for crossing over  
 911 in mammals. *Genet.* **205**, 155-168.

912 [44] Ross-Ibarra, J. 2007 Genome size and recombination in angiosperms: a second look. *J.*  
 913 *Evol. Biol.* **20**, 800-806.

914 [45] Mercier, R, Mézard, C, Jenczewski, E, Macaisne, N & Grelon, M. 2015 The molecular  
 915 biology of meiosis in plants. *Ann. Rev. Plant Biol.* **66**, 297-327.

916 [46] Halkka, O. 1964 Recombination in six Homopterous families. *Evolution* **18**, 81-88.

917 [47] Ross, L, Blackmon, H, Lorite, P, Gokhman, VE & Hardy, NB. 2015 Recombination,  
 918 chromosome number and eusociality in the Hymenoptera. *J. Evol. Biol.* **28**, 105-116.

919 [48] Dumont, BL & Payseur, BA. 2008 Evolution of the genomic rate of recombination in  
 920 mammals. *Evolution* **62**, 276-294.

921 [49] Sax, K. 1934 Variation in chiasma frequency in *Secale*, *Vicia* and *Tradescantia*. *Cytologia*  
 922 **6**, 289-293.

923 [50] Rees, H & Ahmad, K. 1963 Chiasma frequencies in *Iolium* populations. *Evolution* **17**,  
 924 575-579.

925 [51] Slizynski, BM. 1955 Chiasmata in the male mouse. *J. Genet.* **53**, 597-605.

926 [52] Sanchez-Moran, E, Armstrong, SJ, Santos, JL, Franklin, FCH & Jones, GH. 2002 Variation  
 927 in chiasma frequency among eight accessions of *Arabidopsis thaliana*. *Genet.* **162**, 1415-  
 928 1422.

929 [53] Weissman, DB. 1976 Geographical variability in the pericentric inversion system of the  
 930 grasshopper *Trimerotropis pseudofasciata*. *Chromosoma* **55**, 325-347.

931 [54] Price, DJ & Bantock, CR. 1975 Marginal populations of *Cepaea nemoralis* (L.) on the  
 932 brendon hills, England. II. Variation in chiasma frequency. *Evolution* **29**, 278-286.

933 [55] Gibbs, PE, Milne, C & Carrillo, MV. 1975 Correlation between the breeding system and  
 934 recombination index in five species of *Senecio*. *New Phytol.* **75**, 619-626.

935 [56] Zarchi, Y, Simchen, G, Hillel, J & Schaap, T. 1972 Chiasmata and the breeding system in  
 936 wild populations of diploid wheats. *Chromosoma* **38**, 77-94.

937 [57] Gion, J-M, Hudson, CJ, Lesur, I, Vaillancourt, RE, Potts, BM & Freeman, JS. 2016  
 938 Genome-wide variation in recombination rate in *Eucalyptus*. *BMC Genom.* **17**, 590.

939 [58] Kawakami, T, Mugal, CF, Suh, A, Nater, A, Burri, R, Smeds, L & Ellegren, H. 2017 Whole-  
 940 genome patterns of linkage disequilibrium across flycatcher populations clarify the causes  
 941 and consequences of fine-scale recombination rate variation in birds. *Mol. Ecol.*, n/a-n/a.

942 [59] Ross, JA, Koboldt, DC, Staisch, JE, Chamberlin, HM, Gupta, BP, Miller, RD, Baird, SE &  
 943 Haag, ES. 2011 *Caenorhabditis briggsae* recombinant inbred line genotypes reveal inter-  
 944 strain incompatibility and the evolution of recombination. *PLoS Genet.* **7**.

945 [60] Bauer, E, Falque, M, Walter, H, Bauland, C, Camisan, C, Campo, L, Meyer, N, Ranc, N,  
 946 Rincint, R, Schipprack, W, et al. 2013 Intrasppecific variation of recombination rate in maize.  
 947 *Genom. Biol.* **14**, R103.

948 [61] van Oers, K, Santure, AW, De Cauwer, I, van Bers, NEM, Crooijmans, R, Sheldon, BC,  
 949 Visser, ME, Slate, J & Groenen, MAM. 2014 Replicated high-density genetic maps of two

950 great tit populations reveal fine-scale genomic departures from sex-equal recombination  
951 rates. *Heredity* **112**, 307-316.

952 [62] Ross, CR, DeFelice, DS, Hunt, GJ, Ihle, KE, Amdam, GV & Rueppell, O. 2015 Genomic  
953 correlates of recombination rate and its variability across eight recombination maps in the  
954 western honey bee (*Apis mellifera* L.). *BMC Genom.* **16**, 107.

955 [63] Smagulova, F, Brick, K, Pu, Y, Camerini-Otero, RD & Petukhova, GV. 2016 The  
956 evolutionary turnover of recombination hot spots contributes to speciation in mice. *Genes*  
957 *Devel.* **30**, 266-280.

958 [64] Auton, A, Fledel-Alon, A, Pfeifer, S, Venn, O, Séguirel, L, Street, T, Leffler, EM, Bowden,  
959 R, Aneas, I, Broxholme, J, et al. 2012 A fine-scale chimpanzee genetic map from population  
960 sequencing. *Science* **336**, 193-198.

961 [65] Axelsson, E, Webster, MT, Ratnakumar, A, The, LC, Ponting, CP & Lindblad-Toh, K. 2012  
962 Death of PRDM9 coincides with stabilization of the recombination landscape in the dog  
963 genome. *Genome Res.* **22**, 51-63.

964 [66] Lam, I & Keeney, S. 2015 Nonparadoxical evolutionary stability of the recombination  
965 initiation landscape in yeast. *Science* **350**, 932-937.

966 [67] Baker, Z, Schumer, M, Haba, Y, Bashkirova, L, Holland, C, Rosenthal, GG & Przeworski,  
967 M. 2017 Repeated losses of PRDM9-directed recombination despite the conservation of  
968 PRDM9 across vertebrates. *eLife* **6**, e24133.

969 [68] Lenormand, T & Dutheil, J. 2005 Recombination difference between sexes: A role for  
970 haploid selection. *PLoS Biol.* **3**, 396-403.

971 [69] Brandvain, Y & Coop, G. 2012 Scrambling eggs: Meiotic drive and the evolution of  
972 female recombination rates. *Genet.* **190**, 709-723.

973 [70] Hedrick, PW. 2007 Sex: Differences in mutation, recombination, selection, gene flow,  
974 and genetic drift. *Evolution* **61**, 2750-2771.

975 [71] Haldane, JBS. 1922 Sex ratio and unisexual sterility in hybrid animals. *J. Genet.* **12**, 101-  
976 109.

977 [72] Huxley, J. 1928 Sexual difference in linkage in *Gammarus chevreuxi*. *J. Genet.* **20**, 145-  
978 156.

979 [73] Nei, M. 1969 Linkage modification and sex difference in recombination. *Genet.* **63**, 681-  
980 699.

981 [74] Wang, S, Zhang, LL, Meyer, E & Matz, MV. 2009 Construction of a high-resolution  
982 genetic linkage map and comparative genome analysis for the reef-building coral *Acropora*  
983 *millepora*. *Genom. Biol.* **10**, R126.

984 [75] Burt, A, Bell, G & Harvey, PH. 1991 Sex differences in recombination. *J. Evol. Biol.* **4**,  
985 259-277.

986 [76] Singh, ND, Criscoe, DR, Skolfield, S, Kohl, KP, Keebaugh, ES & Schlenke, TA. 2015 Fruit  
987 flies diversify their offspring in response to parasite infection. *Science* **349**, 747-750.

988 [77] Kong, A, Thorleifsson, G, Frigge, ML, Masson, G, Gudbjartsson, DF, Villemoes, R,  
989 Magnusdottir, E, Olafsdottir, SB, Thorsteinsdottir, U & Stefansson, K. 2014 Common and  
990 low-frequency variants associated with genome-wide recombination rate. *Nat. Genet.* **46**,  
991 11-16.

992 [78] Kong, A, Thorleifsson, G, Gudbjartsson, DF, Masson, G, Sigurdsson, A, Jonasdottir, A,  
993 Walters, GB, Jonasdottir, A, Gylfason, A, Kristinsson, KT, et al. 2010 Fine-scale recombination  
994 rate differences between sexes, populations and individuals. *Nature* **467**, 1099-1103.

995 [79] De Storme, N & Geelen, D. 2017 Dynamics of male meiotic recombination frequency  
996 during plant development using Fluorescent Tagged Lines in *Arabidopsis thaliana*. *Sci. Rep.*  
997 **7**, 42535.

998 [80] Bomblies, K, Higgins, JD & Yant, L. 2015 Meiosis evolves: adaptation to external and  
999 internal environments. *New Phytol.* **208**, 306-323.

1000 [81] Stevison, L, Sefick, S, Rushton, C & Graze, R. THIS ISSUE Recombination rate plasticity:  
1001 revealing mechanisms by design. *Phil. Trans. R. Soc. B.*

1002 [82] Martin, HC, Christ, R, Hussin, JG, O'Connell, J, Gordon, S, Mbarek, H, Hottenga, J-J,  
1003 McAloney, K, Willemsen, G, Gasparini, P, et al. 2015 Multicohort analysis of the maternal  
1004 age effect on recombination. *Nat. Comm.* **6**, 7846.

1005 [83] Hussin, J, Roy-Gagnon, M-H, Gendron, R, Andelfinger, G & Awadalla, P. 2011 Age-  
1006 dependent recombination rates in human pedigrees. *PLoS Genet.* **7**, e1002251.

1007 [84] Speed, RM. 1977 The effects of ageing on the meiotic chromosomes of male and  
1008 female mice. *Chromosoma* **64**, 241-254.

1009 [85] Henderson, SA & Edwards, RG. 1968 Chiasma frequency and maternal age in mammals.  
1010 *Nature* **218**, 22-28.

1011 [86] Campbell, CL, Furlotte, NA, Eriksson, N, Hinds, D & Auton, A. 2015 Escape from  
1012 crossover interference increases with maternal age. *Nat. Comm.* **6**, 6260.

1013 [87] Vrooman, LA, Nagaoka, SI, Hassold, TJ & Hunt, PA. 2014 Evidence for paternal age-  
1014 related alterations in meiotic chromosome dynamics in the mouse. *Genet.* **196**, 385-396.

1015 [88] Li, F, De Storme, N & Geelen, D. 2017 Dynamics of male meiotic recombination  
1016 frequency during plant development using Fluorescent Tagged Lines in *Arabidopsis thaliana*.  
1017 *Sci. Rep.* **7**, 42535.

1018 [89] Wang, ZY, Shen, BT, Jiang, JC, Li, JQ & Ma, L. 2016 Effect of sex, age and genetics on  
1019 crossover interference in cattle. *Sci. Rep.* **6**, 37698.

1020 [90] Morgan, CH, Zhang, H & Bomblies, K. THIS ISSUE Are the effects of elevated  
1021 temperature on meiotic recombination and thermotolerance linked via the axis and  
1022 synaptonemal complex? *Phil. Trans. R. Soc. B.*

1023 [91] Phillips, D, Jenkins, G, Macaulay, M, Nibau, C, Wnetrzak, J, Fallding, D, Colas, I, Oakey,  
1024 H, Waugh, R & Ramsay, L. 2015 The effect of temperature on the male and female  
1025 recombination landscape of barley. *New Phytol.* **208**, 421-429.

1026 [92] Salathé, M, Kouyos, RD & Bonhoeffer, S. 2009 On the Causes of Selection for  
1027 Recombination underlying the Red Queen Hypothesis. *Am. Nat.* **174**, S31-S42.

1028 [93] Fischer, O & Schmid-Hempel, P. 2005 Selection by parasites may increase host  
1029 recombination frequency. *Biol. Lett.* **1**, 193-195.

1030 [94] Kerstes, NA, Béréños, C, Schmid-Hempel, P & Wegner, KM. 2012 Antagonistic  
1031 experimental coevolution with a parasite increases host recombination frequency. *BMC*  
1032 *Evol. Biol.* **12**, 18.

1033 [95] Kovalchuk, I, Kovalchuk, O, Kalck, V, Boyko, V, Filkowski, J, Heinlein, M & Hohn, B. 2003  
1034 Pathogen-induced systemic plant signal triggers DNA rearrangements. *Nature* **423**, 760-762.

1035 [96] Andronic, L. 2012 Viruses as triggers of DNA rearrangements in host plants. *Canad. J.*  
1036 *Plant Sc.* **92**, 1083-1091.

1037 [97] Dumont, BL, Devlin, AA, Truempy, DM, Miller, JC & Singh, ND. 2015 No evidence that  
1038 infection alters global recombination rate in house mice. *PLoS ONE* **10**, e0142266.

1039 [98] Greeff, M & Schmid-Hempel, P. 2010 Influence of co-evolution with a parasite, *Nosema*  
1040 *whitei*, and population size on recombination rates and fitness in the red flour beetle,  
1041 *Tribolium castaneum*. *Genetica* **138**, 737-744.

1042 [99] Brachet, E, Sommermeyer, V & Borde, V. 2012 Interplay between modifications of  
1043 chromatin and meiotic recombination hotspots. *Biol. Cell* **104**, 51-69.

1044 [100] Pan, J, Sasaki, M, Kniewel, R, Murakami, H, Blitzblau, Hannah G, Tischfield, Sam E, Zhu,  
1045 X, Neale, Matthew J, Jasin, M, Socci, Nicholas D, et al. 2011 A hierarchical combination of  
1046 factors shapes the genome-wide topography of yeast meiotic recombination initiation. *Cell*  
1047 **144**, 719-731.

1048 [101] Borde, V & de Massy, B. 2013 Programmed induction of DNA double strand breaks  
1049 during meiosis: setting up communication between DNA and the chromosome structure.  
1050 *Curr. Opinion Genet. Develop.* **23**, 147-155.

1051 [102] Moens, PB, Kolas, NK, Tarsounas, M, Marcon, E, Cohen, PE & Spyropoulos, B. 2002 The  
1052 time course and chromosomal localization of recombination-related proteins at meiosis in  
1053 the mouse are compatible with models that can resolve the early DNA-DNA interactions  
1054 without reciprocal recombination. *J. Cell Sci.* **115**, 1611-1622.

1055 [103] Mancera, E, Bourgon, R, Brozzi, A, Huber, W & Steinmetz, LM. 2008 High-resolution  
1056 mapping of meiotic crossovers and non-crossovers in yeast. *Nature* **454**, 479-485.

1057 [104] Gray, MM, Granka, J, Bustamante, CD, Sutter, N, Boyko, A, Zhu, L, Ostrander, E &  
1058 Wayne, R. 2009 Linkage disequilibrium and demographic history of wild and domestic  
1059 canids. *Genet.* **181**, 1493-1505.

1060 [105] Burt, A. 2000 Perspective: Sex, recombination, and the efficacy of selection—was  
1061 Weismann right? *Evolution* **54**, 337-351.

1062 [106] Khan, A, Taylor, S, Su, C, Mackey, AJ, Boyle, J, Cole, R, Glover, D, Tang, K, Paulsen, IT,  
1063 Berriman, M, et al. 2005 Composite genome map and recombination parameters derived  
1064 from three archetypal lineages of *Toxoplasma gondii*. *NAR* **33**, 2980-2992.

1065 [107] Kirkpatrick, M. 2010 How and why chromosome inversions evolve. *PLoS Biol.* **8**,  
1066 e1000501.

1067 [108] Farré, M, Micheletti, D & Ruiz-Herrera, A. 2013 Recombination rates and genomic  
1068 shuffling in human and chimpanzee—a new twist in the chromosomal speciation theory.  
1069 *Mol. Biol. Evol.* **30**, 853-864.

1070 [109] Dumas, D, Catalan, J & Britton-davidian, J. 2015 Reduced recombination patterns in  
1071 Robertsonian hybrids between chromosomal races of the house mouse: chiasma analyses.  
1072 *Heredity* **114**, 56-64.

1073 [110] de Vaio, ES, Goñi, B & Rey, C. 1979 Chromosome polymorphism in populations of the  
1074 grasshopper *Trimerotropis pallidipennis* from southern Argentina. *Chromosoma* **71**, 371-  
1075 386.

1076 [111] Lucchesi, JC & Suzuki, DT. 1968 The interchromosomal control of recombination. *Ann.*  
1077 *Rev. Genet.* **2**, 53-86.

1078 [112] Talbert, PB & Henikoff, S. 2010 Centromeres convert but don't cross. *PLoS Biol.* **8**,  
1079 e1000326.

1080 [113] Petkov, PM, Broman, KW, Szatkiewicz, JP & Paigen, K. 2007 Crossover interference  
1081 underlies sex differences in recombination rates. *Trends Genet.* **23**, 539-542.

1082 [114] Kent, TV, Uzunović, J & Wright, SI. THIS ISSUE Coevolution between transposable  
1083 elements and recombination. *Phil. Trans. R. Soc. B.*

1084 [115] Melamed-Bessudo, C, Shilo, S & Levy, AA. 2016 Meiotic recombination and genome  
1085 evolution in plants. *Curr. Opinion Plant Biol.* **30**, 82-87.

1086 [116] Eyre-Walker, A. 1993 Recombination and mammalian genome evolution. *Proc. Biol.*  
1087 *Sci.* **252**, 237-243.



1088 [117] Marais, G, Mouchiroud, D & Duret, L. 2001 Does recombination improve selection on  
1089 codon usage? Lessons from nematode and fly complete genomes. *Proc. Natl. Acad. Sci.*  
1090 *U.S.A.* **98**, 5688-5692.

1091 [118] Webster, MT, Axelsson, E & Ellegren, H. 2006 Strong Regional Biases in Nucleotide  
1092 Substitution in the Chicken Genome. *Mol. Biol. Evol.* **23**, 1203-1216.

1093 [119] Muyle, A, Serres-Giardi, L, Ressayre, A, Escobar, J & Glémin, S. 2011 GC-Biased Gene  
1094 conversion and selection affect GC content in the *Oryza* genus (rice). *Mol. Biol. Evol.* **28**,  
1095 2695-2706.

1096 [120] Marsolier-Kergoat, M-C & Yeramian, E. 2009 GC content and recombination:  
1097 Reassessing the causal effects for the *Saccharomyces cerevisiae* genome. *Genet.* **183**, 31-38.

1098 [121] Petes, TD & Merker, JD. 2002 Context dependence of meiotic recombination hotspots  
1099 in yeast: The relationship between recombination activity of a reporter construct and base  
1100 composition. *Genet.* **162**, 2049-2052.

1101 [122] Qiao, H, Rao, HBDP, Yang, Y, Fong, JH, Cloutier, JM, Deacon, DC, Nagel, KE, Swartz, RK,  
1102 Strong, E, Holloway, JK, et al. 2014 Antagonistic roles of ubiquitin ligase HEI10 and SUMO  
1103 ligase RNF212 regulate meiotic recombination. *Nat. Genet.* **46**, 194-199.

1104 [123] Ziolkowski, PA, Underwood, CJ, Lambing, C, Martinez-Garcia, M, Lawrence, EJ,  
1105 Ziolkowska, L, Griffin, C, Choi, K, Franklin, FCH & Martienssen, RA. 2017 Natural variation  
1106 and dosage of the HEI10 meiotic E3 ligase control Arabidopsis crossover recombination.  
1107 *Genes Devel.* **31**, 306-317.

1108 [124] Petit, M, Astruc, J-M, Sarry, J, Drouilhet, L, Fabre, S, Moreno, C & Servin, B. 2017  
1109 Variation in recombination rate and its genetic determinism in sheep (*Ovis aries*)  
1110 populations from combining multiple genome-wide datasets. *bioRxiv*.

1111 [125] Reynolds, A, Qiao, H, Yang, Y, Chen, JK, Jackson, N, Biswas, K, Holloway, JK, Baudat, F,  
1112 de Massy, B, Wang, J, et al. 2013 RNF212 is a dosage-sensitive regulator of crossing-over  
1113 during mammalian meiosis. *Nat. Genet.* **45**, 269-278.

1114 [126] Smagulova, F, Gregoret, IV, Brick, K, Khil, P, Camerini-Otero, RD & Petukhova, GV.  
1115 2011 Genome-wide analysis reveals novel molecular features of mouse recombination  
1116 hotspots. *Nature* **472**, 375-378.

1117 [127] Yelina, NE, Ziolkowski, PA, Miller, N, Zhao, X, Kelly, KA, Muñoz, DF, Mann, DJ,  
1118 Copenhaver, GP & Henderson, IR. 2013 High-throughput analysis of meiotic crossover  
1119 frequency and interference via flow cytometry of fluorescent pollen in Arabidopsis thaliana.  
1120 *Nat. Protocols* **8**, 2119-2134.

1121 [128] Lenormand, T, Engelstädter, J, Johnston, SE, Wijnker, E & Haag, CR. 2016 Evolutionary  
1122 mysteries in meiosis. *Phil. Trans. R. Soc. B* **371**.

1123 [129] Kaur, T & Rockman, MV. 2014 Crossover heterogeneity in the absence of hotspots in  
1124 *Caenorhabditis elegans*. *Genet.* **196**, 137-148.

1125 [130] Chung, G, Rose, AM, Petalcorin, MIR, Martin, JS, Kessler, Z, Sanchez-Pulido, L, Ponting,  
1126 CP, Yanowitz, JL & Boulton, SJ. 2015 REC-1 and HIM-5 distribute meiotic crossovers and  
1127 function redundantly in meiotic double-strand break formation in *Caenorhabditis elegans*.  
1128 *Genes Devel.* **29**, 1969-1979.

1129 [131] Kong, A, Barnard, J, Gudbjartsson, DF, Thorleifsson, G, Jonsdottir, G, Sigurdardottir, S,  
1130 Richardsson, B, Jonsdottir, J, Thorgeirsson, T, Frigge, ML, et al. 2004 Recombination rate and  
1131 reproductive success in humans. *Nat. Genet.* **36**, 1203-1206.

1132 [132] Dewees, AA. 1975 Genetic modification of recombination rate in *Tribolium castaneum*.  
1133 *Genet.* **81**, 537-552.

1134 [133] Barton, NH & Servedio, MR. 2015 The interpretation of selection coefficients.  
1135 *Evolution* **69**, 1101-1112.

1136 [134] Dapper, AL & Payseur, BA. THIS ISSUE Connecting theory and data in recombination  
1137 rate evolution. *Phil. Trans. R. Soc. B*.

1138 [135] Felsenstein, J. 1974 The evolutionary advantage of recombination. *Genet.* **78**, 737-756.

1139 [136] Otto, SP & Barton, NH. 2001 Selection for recombination in small populations.  
1140 *Evolution* **55**, 1921-1931.

1141 [137] Lenormand, T & Otto, SP. 2000 The Evolution of recombination in a heterogeneous  
1142 environment. *Genet.* **156**, 423-438.

1143 [138] Ellegren, H & Galtier, N. 2016 Determinants of genetic diversity. *Nat. Rev. Genet.* **17**,  
1144 422-433.

1145 [139] Hill, WG & Robertson, A. 1966 The effect of linkage on limits to artificial selection.  
1146 *Genetical Res.* **8**, 269-294.

1147 [140] Burt, A & Bell, G. 1987 Mammalian chiasma frequencies as a test of two theories of  
1148 recombination. *Nature* **326**, 803-805.

1149 [141] Stebbins, GL. 1950 *Variation and evolution in plants*. New York, Columbia.

1150 [142] Chiang, T, Schultz, RM & Lampson, MA. 2012 Meiotic origins of maternal age-related  
1151 aneuploidy. *Biol. Reprod.* **86**, 3.

1152 [143] Aggarwal, DD, Rashkovetsky, E, Michalak, P, Cohen, I, Ronin, Y, Zhou, D, Haddad, GG &  
1153 Korol, AB. 2015 Experimental evolution of recombination and crossover interference in  
1154 *Drosophila* caused by directional selection for stress-related traits. *BMC Biol.* **13**, 101.

1155 [144] Korol, AB & Iliadi, KG. 1994 Increased recombination frequencies resulting from  
1156 directional selection for geotaxis in *Drosophila*. *Heredity* **72**, 64-68.

1157 [145] Ross-Ibarra, J. 2004 The evolution of recombination under domestication: A test of  
1158 two hypotheses. *Am. Nat.* **163**, 105-112.

1159 [146] Muñoz-Fuentes, V, Marcet-Ortega, M, Alkorta-Aranburu, G, Forsberg, CL, Morrell, JM,  
1160 Manzano-Piedras, E, Söderberg, A, Daniel, K, Villalba, A, Toth, A, et al. 2014 Strong artificial  
1161 selection in domestic mammals did not result in an increased recombination rate. *Mol. Biol.*  
1162 *Evol.* **32**, 510-523.

1163 [147] Otto, SP & Michalakakis, Y. 1998 The evolution of recombination in changing  
1164 environments. *Trends Ecol. Evol.* **13**, 145-151.

1165 [148] Dapper, AL & Lively, CM. 2014 Inter-locus sexually antagonistic coevolution can create  
1166 indirect selection for increased recombination. *Evolution* **68**, 1216-1224.

1167 [149] Fulton, JE, McCarron, AM, Lund, AR, Pinegar, KN, Wolc, A, Chazara, O, Bed'Hom, B,  
1168 Berres, M & Miller, MM. 2016 A high-density SNP panel reveals extensive diversity, frequent  
1169 recombination and multiple recombination hotspots within the chicken major  
1170 histocompatibility complex B region between BG2 and CD1A1. *Genet. Sel. Evol.* **48**, 1.

1171 [150] Choi, K, Reinhard, C, Serra, H, Ziolkowski, PA, Underwood, CJ, Zhao, X, Hardcastle, TJ,  
1172 Yelina, NE, Griffin, C, Jackson, M, et al. 2016 Recombination rate heterogeneity within  
1173 *Arabidopsis* disease resistance genes. *PLoS Genet.* **12**, e1006179.

1174 [151] Market, E & Papavasiliou, FN. 2003 V(D)J Recombination and the Evolution of the  
1175 Adaptive Immune System. *PLoS Biol.* **1**, e16.

1176 [152] Salathé, M, Kouyos, RD, Regoes, RR, Bonhoeffer, S & Van Baalen, M. 2008 Rapid  
1177 parasite adaptation drives selection for high recombination rates. *Evolution* **62**, 295-300.

1178 [153] Petrov, DA. 2001 Evolution of genome size: new approaches to an old problem. *Trends*  
1179 *Genet.* **17**, 23-28.

1180 [154] Wright, SI. 2001 Evolution of Genome Size. In *eLS* (John Wiley & Sons, Ltd).

1181 [155] Alves, I, Houle, AA, Hussin, JG & Awadalla, P. THIS ISSUE The impact of recombination  
1182 on genome variation, mutation load and disease. *Phil. Trans. R. Soc. B.*  
1183 [156] Cvetković, D & Tucić, N. 1986 Female recombination rates and fitness in *Drosophila*  
1184 *melanogaster*. *J. Zool. Sys. Evol. Res.* **24**, 198-207.  
1185 [157] Tucić, N, Ayala, FJ & Marinković, D. 1981 Correlation between recombination  
1186 frequency and fitness in *Drosophila melanogaster*. *Genetica* **56**, 61-69.  
1187 [158] Tigano, A & Friesen, VL. 2016 Genomics of local adaptation with gene flow. n/a-n/a.  
1188 [159] Yeaman, S. 2013 Genomic rearrangements and the evolution of clusters of locally  
1189 adaptive loci. *Proc. Natl. Acad. Sci. U.S.A.* **110**, E1743-E1751.  
1190 [160] Thompson, MJ & Jiggins, CD. 2014 Supergenes and their role in evolution. *Heredity*  
1191 **113**, 1-8.  
1192 [161] Feder, JL, Egan, SP & Nosil, P. 2012 The genomics of speciation-with-gene-flow. *Trends*  
1193 *Genet.* **28**, 342-350.  
1194 [162] Lenormand, T. 2003 The Evolution of Sex Dimorphism in Recombination. *Genet.* **163**,  
1195 811-822.  
1196 [163] Mank, JE. 2009 The evolution of heterochiasmy: the role of sexual selection and sperm  
1197 competition in determining sex-specific recombination rates in eutherian mammals. *Genet.*  
1198 *Res.* **91**, 355-363.  
1199 [164] Haig, D & Grafen, A. 1991 Genetic scrambling as a defence against meiotic drive. *J.*  
1200 *Theor. Biol.* **153**, 531-558.  
1201 [165] Chmátal, L, Gabriel, Sofia I, Mitsainas, George P, Martínez-Vargas, J, Ventura, J, Searle,  
1202 Jeremy B, Schultz, Richard M & Lampson, Michael A. 2014 Centromere strength provides  
1203 the cell biological basis for meiotic drive and karyotype evolution in mice. *Curr. Biol.* **24**,  
1204 2295-2300.  
1205 [166] Ball, A, Stapley, J, Dawson, D, Birkhead, T, Burke, T & Slate, J. 2010 A comparison of  
1206 SNPs and microsatellites as linkage mapping markers: lessons from the zebra finch  
1207 (*Taeniopygia guttata*). *BMC Genom.* **11**, 218.  
1208 [167] Slate, J. 2008 Robustness of linkage maps in natural populations: a simulation study.  
1209 *Proc. R. Soc. Lond., B, Biol. Sci.* **275**, 695-702.  
1210 [168] Stumpf, MPH & McVean, GAT. 2003 Estimating recombination rates from population-  
1211 genetic data. *Nat. Rev. Genet.* **4**, 959-968.  
1212 [169] Chan, AH, Jenkins, PA & Song, YS. 2012 Genome-wide fine-scale recombination rate  
1213 variation in *Drosophila melanogaster*. *PLoS Genet.* **8**, e1003090.  
1214 [170] Beeravolu Reddy, C, Hickerson, MJ, Frantz, LAF & Lohse, K. 2016 Approximate  
1215 likelihood inference of complex population histories and recombination from multiple  
1216 genomes. *bioRxiv*.  
1217 [171] Stapley, J, Birkhead, TR, Burke, T & Slate, J. 2010 Pronounced inter- and  
1218 intrachromosomal variation in linkage disequilibrium across the zebra finch genome.  
1219 *Genome Res.* **20**, 496-502.  
1220 [172] Odenthal-Hesse, L, Berg, IL, Veselis, A, Jeffreys, AJ & May, CA. 2014 Transmission  
1221 distortion affecting human noncrossover but not crossover recombination: A hidden source  
1222 of meiotic drive. *PLoS Genet.* **10**, e1004106.  
1223 [173] Xu, S, Ackerman, MS, Long, H, Bright, L, Spitze, K, Ramsdell, JS, Thomas, WK & Lynch,  
1224 M. 2015 A male-specific genetic map of the microcrustacean *Daphnia pulex* based on single-  
1225 sperm whole-genome sequencing. *Genet.* **201**, 31-38.  
1226 [174] Nam, K & Ellegren, H. 2012 Recombination Drives Vertebrate Genome Contraction.  
1227 *PLoS Genet.* **8**, e1002680.

1228 [175] Archie, JP. 1981 Mathematic coupling of data: a common source of error. *Ann. Surgery*  
1229 **193**, 296-303.

1230 [176] Capilla, L, Garcia Caldés, M & Ruiz-Herrera, A. 2016 Mammalian Meiotic  
1231 Recombination: A Toolbox for Genome Evolution. *Cytogen. Genome Res.* **150**, 1-16.

1232 [177] Haag, CR, Theodosiou, L, Zahab, R & Lenormand, T. THIS ISSUE Low recombination  
1233 rates in sexual species and sex-asex transitions. *Phil. Trans. R. Soc. B.*

1234 [178] Backström, N, Forstmeier, W, Schielzeth, H, Mellenius, H, Nam, K, Bolund, E, Webster,  
1235 MT, Öñst, T, Schneider, M, Kempenaers, B, et al. 2010 The recombination landscape of the  
1236 zebra finch *Taeniopygia guttata* genome. *Genome Res.* **20**, 485-495.

1237 [179] Escudero, M, Hipp, AL, Hansen, TF, Voje, KL & Luceño, M. 2012 Selection and inertia in  
1238 the evolution of holocentric chromosomes in sedges (Carex, Cyperaceae). *New Phytol.* **195**,  
1239 237-247.

1240 [180] Yant, L, Hollister, Jesse D, Wright, Kevin M, Arnold, Brian J, Higgins, James D, Franklin,  
1241 FChris H & Bomblies, K. 2013 Meiotic adaptation to genome duplication in *Arabidopsis*  
1242 *arenosa*. *Curr. Biol.* **23**, 2151-2156.

1243 [181] Bomblies, K, Jones, G, Franklin, C, Zickler, D & Kleckner, N. 2016 The challenge of  
1244 evolving stable polyploidy: could an increase in “crossover interference distance” play a  
1245 central role? *Chromosoma* **125**, 287-300.

1246 [182] Anderson, AR, Hoffmann, AA, McKechnie, SW, Umina, PA & Weeks, AR. 2005 The  
1247 latitudinal cline in the In(3R)Payne inversion polymorphism has shifted in the last 20 years in  
1248 Australian *Drosophila melanogaster* populations. *Mol. Ecol.* **14**, 851-858.

1249 [183] Cheng, C, White, BJ, Kamdem, C, Mockaitis, K, Costantini, C, Hahn, MW & Besansky,  
1250 NJ. 2012 Ecological genomics of *Anopheles gambiae* along a latitudinal cline: a population-  
1251 resequencing approach. *Genet.* **190**, 1417-1432.

1252 [184] Wellenreuther, M, Rosenquist, H, Jaksons, P & Larson, KW. 2017 Local adaptation  
1253 along an environmental cline in a species with an inversion polymorphism. *J. Evol. Biol.* **30**,  
1254 1068-1077.

1255 [185] Stefansson, H, Helgason, A, Thorleifsson, G, Steinthorsdottir, V, Masson, G, Barnard, J,  
1256 Baker, A, Jonasdottir, A, Ingason, A, Gudnadottir, VG, et al. 2005 A common inversion under  
1257 selection in Europeans. *Nat. Genet.* **37**, 129-137.

1258 [186] Joron, M, Frezal, L, Jones, RT, Chamberlain, NL, Lee, SF, Haag, CR, Whibley, A, Becuwe,  
1259 M, Baxter, SW, Ferguson, L, et al. 2011 Chromosomal rearrangements maintain a  
1260 polymorphic supergene controlling butterfly mimicry. *Nature* **477**, 203-206.

1261 [187] Jones, FC, Grabherr, MG, Chan, YF, Russell, P, Mauceli, E, Johnson, J, Swofford, R,  
1262 Pirun, M, Zody, MC, White, S, et al. 2012 The genomic basis of adaptive evolution in  
1263 threespine sticklebacks. *Nature* **484**, 55–61.

1264 [188] Berg, PR, Jentoft, S, Star, B, Ring, KH, Knutsen, H, Lien, S, Jakobsen, KS & André, C.  
1265 2015 Adaptation to low salinity promotes genomic divergence in Atlantic cod (*Gadus*  
1266 *morhua* L.). *Genom. Biol. Evol.* **7**, 1644-1663.

1267 [189] Twyford, AD & Friedman, J. 2015 Adaptive divergence in the monkey flower *Mimulus*  
1268 *guttatus* is maintained by a chromosomal inversion. *Evolution* **69**, 1476-1486.

1269 [190] Wadsworth, CB, Li, X & Dopman, EB. 2015 A recombination suppressor contributes to  
1270 ecological speciation in OSTRINIA moths. *Heredity* **114**, 593-600.

1271 [191] Lee, C-R, Wang, B, Mojica, JP, Mandáková, T, Prasad, KVSK, Goicoechea, JL, Perera, N,  
1272 Hellsten, U, Hundley, HN, Johnson, J, et al. 2017 Young inversion with multiple linked QTLs  
1273 under selection in a hybrid zone. *Nat. Ecol. Evol.* **1**, 0119.

1274 [192] Kitano, J, Ross, JA, Mori, S, Kume, M, Jones, FC, Chan, YF, Absher, DM, Grimwood, J,  
 1275 Schmutz, J, Myers, RM, et al. 2009 A role for a neo-sex chromosome in stickleback  
 1276 speciation. *Nature* **461**, 1079-1083.  
 1277 [193] Balcova, M, Faltusova, B, Gergelits, V, Bhattacharyya, T, Mihola, O, Trachtulec, Z,  
 1278 Knopf, C, Fotopulosova, V, Chvatalova, I, Gregorova, S, et al. 2016 Hybrid sterility locus on  
 1279 chromosome X controls meiotic recombination rate in mouse. *PLoS Genet.* **12**, e1005906.  
 1280 [194] Ayala, D, Fontaine, MC, Cohuet, A, Fontenille, D, Vitalis, R & Simard, F. 2011  
 1281 Chromosomal inversions, natural selection and adaptation in the malaria vector *Anopheles*  
 1282 *funestus*. *Mol. Biol. Evol.* **28**, 745-758.  
 1283 [195] Michel, AP, Sim, S, Powell, THQ, Taylor, MS, Nosil, P & Feder, JL. 2010 Widespread  
 1284 genomic divergence during sympatric speciation. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 9724-  
 1285 9729.  
 1286 [196] McGaugh, SE & Noor, MAF. 2012 Genomic impacts of chromosomal inversions in  
 1287 parapatric *Drosophila* species. *Phil. Trans. R. Soc. B* **367**, 422-429.  
 1288 [197] Britton-Davidian, J, Caminade, P, Davidian, E & Pagès, M. 2017 Does chromosomal  
 1289 change restrict gene flow between house mouse populations (*Mus musculus domesticus*)?  
 1290 Evidence from microsatellite polymorphisms. *Biol. J. Linn. Soc.* **122**, 224-240.  
 1291 [198] Gould, BA, Chen, Y & Lowry, DB. 2017 Pooled ecotype sequencing reveals candidate  
 1292 genetic mechanisms for adaptive differentiation and reproductive isolation. *Mol. Ecol.* **26**,  
 1293 163-177.  
 1294 [199] Turner, TL, Hahn, MW & Nuzhdin, SV. 2005 Genomic islands of speciation in *Anopheles*  
 1295 *gambiae*. *PLoS Biol.* **3**, e285.  
 1296 [200] Gante, HF, Matschiner, M, Malmstrøm, M, Jakobsen, KS, Jentoft, S & Salzburger, W.  
 1297 2016 Genomics of speciation and introgression in Princess cichlid fishes from Lake  
 1298 Tanganyika. *Mol. Ecol.* **25**, 6143-6161.  
 1299 [201] Carneiro, M, Albert, FW, Afonso, S, Pereira, RJ, Burbano, H, Campos, R, Melo-Ferreira,  
 1300 J, Blanco-Aguilar, JA, Villafuerte, R, Nachman, MW, et al. 2014 The genomic architecture of  
 1301 population divergence between subspecies of the European Rabbit. *PLoS Genet.* **10**,  
 1302 e1003519.  
 1303 [202] Crawford, JE, Riehle, MM, Guelbeogo, WM, Gneme, A, Sagnon, NF, Vernick, KD,  
 1304 Nielsen, R & Lazzaro, BP. 2015 Reticulate speciation and barriers to introgression in the  
 1305 *Anopheles gambiae* species complex. *Genom. Biol. Evol.* **7**, 3116-3131.  
 1306 [203] Brandvain, Y, Kenney, AM, Flagel, L, Coop, G & Sweigart, AL. 2014 Speciation and  
 1307 introgression between *Mimulus nasutus* and *Mimulus guttatus*. *PLoS Genet.* **10**, e1004410.  
 1308 [204] Burri, R, Nater, A, Kawakami, T, Mugal, CF, Olason, PI, Smeds, L, Suh, A, Dutoit, L,  
 1309 Bures, S, Garamszegi, LZ, et al. 2015 Linked selection and recombination rate variation drive  
 1310 the evolution of the genomic landscape of differentiation across the speciation continuum  
 1311 of *Ficedula* flycatchers. *Genome Res.* **25**, 1656-1665.  
 1312 [205] Feulner, PGD, Chain, FJJ, Panchal, M, Huang, Y, Eizaguirre, C, Kalbe, M, Lenz, TL,  
 1313 Samonte, IE, Stoll, M, Bornberg-Bauer, E, et al. 2015 Genomics of divergence along a  
 1314 continuum of parapatric population differentiation. *PLoS Genet.* **11**, e1004966.  
 1315 [206] Vijay, N, Bossu, CM, Poelstra, JW, Weissensteiner, MH, Suh, A, Kryukov, AP & Wolf,  
 1316 JBW. 2016 Evolution of heterogeneous genome differentiation across multiple contact  
 1317 zones in a crow species complex. *Nat. Comm.* **7**, 13195.  
 1318 [207] Wang, J, Street, NR, Scofield, DG & Ingvarsson, PK. 2016 Variation in linked selection  
 1319 and recombination drive genomic divergence during allopatric speciation of European and  
 1320 American aspens. *Mol. Biol. Evol.* **33**, 1754-1767.

1321 [208] Han, F, Lamichhaney, S, Grant, BR, Grant, PR, Andersson, L & Webster, MT. 2017 Gene  
1322 flow, ancient polymorphism, and ecological adaptation shape the genomic landscape of  
1323 divergence among Darwin's finches. *Genome Res.* **27**, 1004-1015.

1324 [209] Renaut, S, Grassa, CJ, Yeaman, S, Moyers, BT, Lai, Z, Kane, NC, Bowers, JE, Burke, JM &  
1325 Rieseberg, LH. 2013 Genomic islands of divergence are not affected by geography of  
1326 speciation in sunflowers. *Nat. Comm.* **4**, 1827.

1327 [210] Phifer-Rixey, M, Bomhoff, M & Nachman, MW. 2014 Genome-wide patterns of  
1328 differentiation among house mouse subspecies. *Genet.* **198**, 283-297.

1329 [211] Keinan, A & Reich, D. 2010 Human population differentiation is strongly correlated  
1330 with local recombination rate. *PLoS Genet.* **6**, e1000886.

1331 [212] Roesti, M, Moser, D & Berner, D. 2013 Recombination in the threespine stickleback  
1332 genome—patterns and consequences. *Mol. Ecol.* **22**, 3014-3027.

1333 [213] Janoušek, V, Munclinger, P, Wang, L, Teeter, KC & Tucker, PK. 2015 Functional  
1334 organization of the genome may shape the species boundary in the house mouse. *Mol. Biol.*  
1335 *Evol.* **32**, 1208-1220.

1336 [214] Samuk, K, Owens, GL, Delmore, KE, Miller, S, Rennison, DJ & Schluter, D. 2017 Gene  
1337 flow and selection interact to promote adaptive divergence in regions of low recombination.  
1338 *Mol. Ecol.* **26**, 4378-4390.

1339